FOX CHASE CANCER CENTER
TEMPLE HEALTH

GI-063 *Phase I Study Of Drug-Eluting Irinotecan Beads (Debiri) In Refractory Metastatic Colorectal Cancer With Liver-Only Or Liver-Predominant Disease.*

IDE Number: G100031/S009

Principal Investigator
Efrat Dotan, M.D.
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
Tel: 215-728-2450
Fax: 215-214-3229
Email: Efrat.dotan@fccc.edu

Co-Investigator
Gary Cohen, M.D.
Temple University
3401 North Broad Street
Philadelphia, PA 19140
Tel: (215) 707-4723
Fax: (215) 707-2428
Email: Gary.Cohen@tuhs.temple.edu

Statistician
Karthik Devarajan, Ph.D.
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
Tel: 215-728-2794
Fax: 215-728-2553
Email: Karthik.Devarajan@fccc.edu

Sub-Investigators
Juhi Mittal, MD
Joseph Panaro, MD
Mark Burshteyn, MD
Emily Cuthbertson, MD
David Pryluck, MD
Dmitry Niman, MD

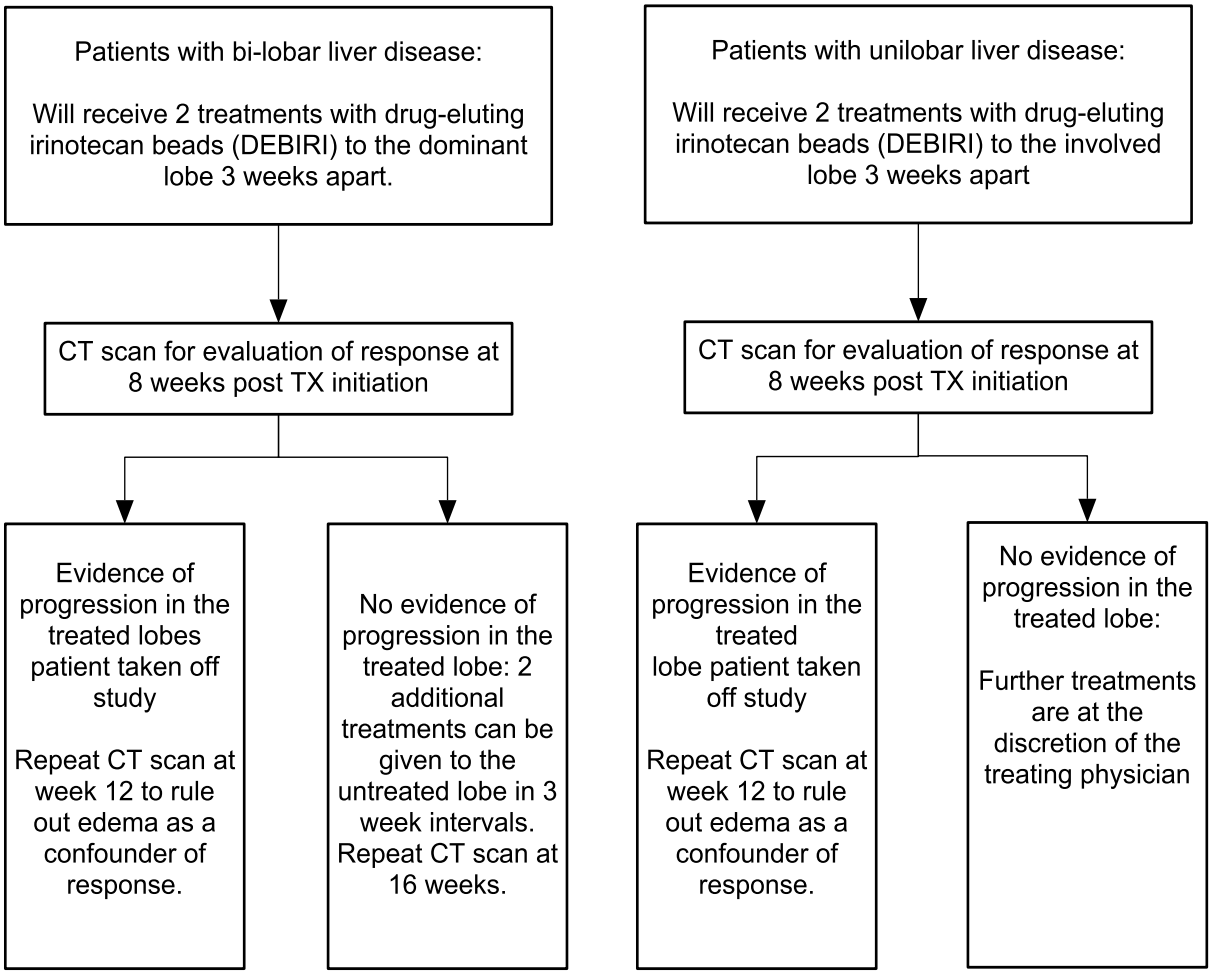
Version Date: November 29, 2013
Amendment 1: October 9, 2015
Amendment 2: February 27, 2017

Schema

Dose Escalation Schedule	
Dose Level	Dose of Irinotecan
Level 1	50 mg per dose
Level 2	75 mg per dose
Level 3	100 mg per dose

Each patient will be treated with a maximum of two treatments per affected lobe.
Cohort will be expanded at the Maximum Tolerated Dose.
The below Schema will be followed at each dose level.

Refractory metastatic colorectal cancer patients with liver only or liver predominant disease.



Contents

1.0 Introduction

Liver metastases secondary to colorectal cancer continue to pose a therapeutic challenge for oncologists. Since the liver is the most common site of metastatic disease in colorectal cancer, it is reasonable to consider local therapy in these circumstances. Surgical resection of liver metastases has been proven to prolong survival in patients with colorectal cancer (1). Several studies have been conducted to study the role of various intra-hepatic therapies for these tumors. In recent years, irinotecan drug eluting beads **(DEBIRI)** have been introduced to the market for local therapy of liver metastases from colorectal cancer. The dose used in practice has not been subjected to a formal evaluation for identification of the maximum tolerated dose. Therefore, we propose a phase I study to determine the maximum tolerated dose of drug eluting irinotecan beads for local treatment of refractory colorectal liver metastases.

1.1 Colorectal cancer – systemic therapy

Colorectal cancer is the second leading cause of cancer death in the United States, with nearly 150,000 cases yearly (2). For many years, standard therapy for advanced colorectal cancer consisted of 5-fluorouracil (5-FU) modulated by leucovorin (LV), with antitumor response rates of 15-20% and median survival of approximately one year (3). Recently, the addition of either irinotecan or oxaliplatin to fluoropyrimidine therapy has resulted in improved response rates of 40-50%, with median survival exceeding 18 months. Single agent irinotecan treatment in 5-FU refractory patients was found to be effective with reported response rates of about 10% (4, 5). Therapies targeting the vascular endothelial growth factor and epidermal growth factor receptor (EGFR) further improve outcome (6-10).

Despite progress with systemic therapy, the vast majority of patients with metastatic colorectal cancer (mCRC) will die from disease. The liver is the most common site of metastatic spread for colorectal cancer. Studies have shown that resection of liver metastases from colorectal cancer can be curative (11). Unfortunately, only a small fraction of patients with metastases confined to the liver are able to undergo curative surgery. Thus, there is significant interest in the development of liver-directed therapies, which could potentially spare the patient toxicities associated with systemic treatment, and improve their survival. Intrahepatic therapy takes advantage of the dual blood supply of the liver. While most normal liver receives blood flow from the portal venous circulation, malignant liver tumors receive the majority of their blood supply from the hepatic artery (12).

1.2 Rationale for intrahepatic therapy in colorectal cancer

An expanding body of literature is available supporting the use of liver-directed therapy in metastatic colorectal cancer. Several investigations of intra-hepatic chemotherapy in colorectal cancer have been undertaken, with the most frequently utilized agent being 5- fluoro-2'-deoxyuridine (FUDR). A meta-analysis comparing systemic to intra-hepatic chemotherapy concluded that intra-hepatic therapy improves the antitumor response rate in liver (13). However, when trials containing only fluoropyrimidine in both arms were assessed, no impact on overall survival was demonstrated. More recently, a randomized study comparing intra-hepatic FUDR to systemic therapy in patients with metastatic colorectal cancer confined to liver demonstrated a small but significant survival benefit of FUDR over systemic 5-FU alone (14). Expanding experience with intra-hepatic FUDR suggests that it can be administered safely with systemic irinotecan or oxaliplatin (15-18). However, intra-hepatic chemotherapy requires surgical placement of an infusion pump, which limits its widespread adoption and applicability. Furthermore, small but clinically meaningful subgroups of patients suffer irreversible biliary injury with FUDR therapy.

Other techniques for localized therapy including radiofrequency ablation, stereotactic radiosurgery, cryotherapy and arterial chemoembolization have been attempted with various results and less toxicity than

intrahepatic chemotherapy (19). Trans-arterial chemoembolization (TACE) has gained renewed interest in recent years. This technique consists of delivery of high concentrations of chemotherapeutic agents to the tumor bed followed by embolization. The embolization is performed to induce oxygen and nutrient depletion to the tumor while minimizing the chemotherapy wash-out. Using this method the extent of systemic toxicity is reduced significantly. This approach has been studied in mCRC with reports of up to 50% response rates (20-27).

1.3 Drug Eluting Irinotecan Beads (DEBIRI) – preliminary data:

Preliminary studies have evaluated the use of drug-eluting chemotherapy beads (DEB) for localized treatment of hepatocellular carcinoma (HCC) and colorectal liver metastases. These beads are not intended to occlude the vessel, but rather locally deliver cytotoxic therapy, resulting in increased intra-tumoral drug concentrations with decreased systemic exposure (19). The use of drug-eluting beads can provide a higher concentration of irinotecan in the liver without the need of a surgically implanted delivery pump and can be an outpatient procedure. These beads obviate the need for an oil/chemotherapy suspension, thus facilitating the handling and delivery and achieving TACE in a simpler one-step procedure (28, 29).

The concept of DEB was initially introduced in patients with HCC using doxorubicin DEB (30). Varela et al evaluated the use of TACE with doxorubicin DEB in 27 patients with HCC and Child score A (31). The procedure was well tolerated, with high response rates of 75%, and 2 year survival rates of 88.9%. Similar results were seen by Malagari et al in patients with unresectable HCC and Child score A or B, with about an 80% response rate and good tolerance to the procedure (32, 33). The use of doxorubicin DEB was also tested following radiofrequency ablation of a solitary unresectable HCC (34). In 12 of 20 treated patients (60%), complete response was seen following treatment with doxorubicin DEB. Lammer et al thus conducted a randomized phase II study of 212 patients with Child-Pugh A or B cirrhosis and unresectable HCC, comparing doxorubicin DEB with conventional chemoembolization with doxorubicin. Objective responses were higher in the doxorubicin DEB arm compared to conventional TACE (52% versus 44% respectively), with marked decrease in toxicity (35). A separate group reported improvement in overall survival among patients with unresectable HCC and Child-Pugh A or B treated with doxorubicin DEB compared to conventional TACE (36). Van Malenstein et al randomly assigned 30 patients to receive either doxorubicin DEB or TACE. The study showed DEB led to lower plasma levels of the cytotoxic drug and minimized toxicity while having a comparable tumor response (37). Song et al compared 60 HCC patients who underwent TACE with DEB to 69 patients who received conventional TACE. The results showed that patients given the DEB treatment resulted in a significantly improved treatment response and longer time to progression while having comparable liver toxicity (38).

Irinotecan drug-eluting beads (DEBIRI) were tested *in vitro* and in rat models with colorectal cancer liver metastases and were found to be have anti-tumor activity, with a favorable safety profile (39, 40). Preclinical histopathology studies revealed that with DEBIRI results in a predicted necrotizing vasculopathy in the arteries/arterioles containing beads, and a granulomatous inflammatory reaction around the beads which is typical of embolization without significant hepatocellular damage (29). A feasibility study by Aliberti et al using DEBIRI in 10 patients with liver metastases from colon cancer utilized a dose of 100 mg every 3 weeks and found this treatment to be well tolerated (41). The study found a significant reduction in CEA level and lesion enhancement in imaging 30 days following the treatment. Side effects included right upper quadrant/right shoulder pain requiring analgesics, vomiting, and alopecia (41). Similar results were presented by Martin and colleagues using DEBIRI on 55 patients with refractory metastatic colorectal cancer (42).

A preliminary clinical trial evaluating treatment with DEBIRI in the setting of metastatic colorectal cancer to the liver found high response rates (~80%), reduction in lesion contrast enhancement on imaging and acceptable toxicity (43). Prophylactic therapy with antibiotics, anti-emetics, dexamethasone and intravenous

hydration was recommended to improve the tolerance of the procedure. A phase II study of DEBIRI in 82 patients with refractory mCRC confirmed an approximately 80% response rate (44). The majority of patients experienced self-limited tolerable nausea, fever, and abdominal pain.

A multi-institutional Phase III study randomized 74 patients with hepatic metastases from colorectal cancer to receive DEBIRI versus systemic FOLFIRI The difference was statistically significant, median survival was 22 months for DEBIRI and 15 months for FOLFIRI. Progression free survival was also significantly better for DEBIRI (7 months versus 4 months) as was median duration of improvement in quality of life (8 months versus 3 months in the FOLFIRI group (45). The DEBIRI group reported a manageable adverse event profile for the DEBIRI therapy. The most common grade 2-3 toxicities seen with DEBIRI were: abdominal pain – 30%, vomiting- 25% and asthenia- 20%. The investigators followed the changes in liver function tests following therapy: 58% of patients had elevation of liver function tests to values greater than 3 times the upper limit of normal. In addition 18% had elevation of bilirubin. All values normalized after 3 weeks in time for the next scheduled therapy. There were no dose reductions or treatment delays among the patients receiving DEBIRI.

The group led by Martin recently published both registry data and a prospective, multicenter, single-arm study administrating DEBIRI as liver directed therapy for metastatic colorectal patients (46-48). The group published their efficacy results of 55 patients with previously treated mCRC to the liver who received a total of 99 DEBIRI treatments (47). The overall 3 month response rate was 65% with 12% of patients having complete response and 53% showing partial response. These outcomes where durable since at 12 month follow up 15% of the patients demonstrated complete response, 25% partial response and 42% stable disease. Overall median progression free survival was 11 months, with a hepatic specific progression free survival of 15 months. The overall survival seen in this heavily pre-treated cohort was 19 months.

Tolerability of DEBIRI was reported in a large cohort of 109 patients treated for various hepatic malignancies, of which 76% had metastatic colorectal cancer (48). Patients in this cohort were treated with a median dose of 100 mg of irinotecan (range 100-200 mg) to a single lobe and a median number of treatments of 2 (range 1-5). Patients with bilobar disease received treatment every two weeks alternating between affected lobes. Adverse events occurred in 20% of patients and were mostly grade 2. Post-embolic syndrome including nausea, vomiting and abdominal pain was the most frequent adverse event documented. Additional common adverse events included hypertension, gastritis, dehydration, anorexia and anemia.

Of 109 patients, four deaths were judged as at least possibly related to treatment (two from gastrointestinal bleeding and two from hepatic dysfunction). Through a multivariate analysis the authors identified 4 factors that could predict for development of adverse events: (1) Lack of use of hepatic arterial lidocaine; (2) >3 treatments; (3) Stasis; (4) >100mg in 1 treatment dose; and (5) bilirubin >2.0 with >50% liver involvement (48). The authors concluded that DEBIRI can be safely used to treat carefully selected patients with metastatic liver disease.

Given efficacy in refractory disease, Martin et al reported the safety, efficacy and tolerability profile of DEBIRI in combination with systemic FOLFOX in the treatment of 10 chemotherapy naïve patients with unresectable hepatic metastases from colorectal cancer. All 10 patients received at least 12 cycles of FOLFOX and 2 treatments with DEBIRI. The initial 9 and 12 month response rates were 100% (2 CR, 8 PR). Four (40%) patients could eventually undergo resection and/or ablation and had median overall survival of 15.2 months. Only 1 severe procedure related adverse event was reported – a grade 3 hypertensive episode requiring overnight hospital observation. DEBIRI was overall well tolerated (49).

1.4 Drug Eluting Irinotecan Beads (DEBIRI) – previous experience at Fox Chase Cancer Center:

Given the encouraging results at select centers, we initiated a phase II study to evaluate the role of DEBIRI for local treatment of refractory colorectal cancer with liver only or liver predominant metastatic disease. Four patients were enrolled on the study in 2011 and treated with intra-hepatic DEBIRI at 100 mg per treatment. Patients received DEBIRI treatment every 3 weeks. Three of the four patients experienced grade 3 elevation of alkaline phosphatase consistent with the protocol defined dose limiting toxicity and requiring premature closure of the study by the data safety monitoring committee. One of four patients had stable disease in the treated lobe after two treatments. The patient's untreated lobe progressed and he remained on study to receive treatment to that site. The patient's staging scan after two additional treatments showed progressive disease and he was taken of study. Table 1 summarizes the outcomes of these patients.

Table 1: FCCC previous experience with DEBIRI:

Patient #	Alk Phos level pre-treatment	Timing of grade 3 Alk Phos elevation	Outcome following Alk Phos elevation	Number of treatments	Overall response
1	144	-	-	2 to each lobe, 4 total treatments	SD – right lobe PD- left lobe
2	137	DAY 64	ERCP & STENT	2	PD
3	225	DAY 14	DIED FROM PD	1	PD
4	473	DAY 1	PD	1	PD

Alk phos- Alkaline phosphatase; PD- Progressive disease; ERCP- Endoscopic retrograde cholangiopancreatography;

Transient elevation of liver function tests is commonly seen following liver directed therapy. In an early study of chemoembolization among patients with hepatocellular carcinoma, these transient changes were seen in all treated patients (1). These adverse events were also documented in the Precision V study comparing DC beads and TACE for hepatocellular carcinoma. Liver function tests on average doubled following DC bead therapy and more than tripled after TACE treatment. As described above, the recent phase III study by Fiorentini et al comparing DEBIRI with systemic FOLFIRI reported transient elevation of liver function tests in 58% of DEBIRI treated patients (45). With these data in mind, liver function test increases are commonly noted in the few weeks immediately following this procedure but they are nearly always transient and rarely indicative of significant irreversible liver injury.

It is possible that the alkaline phosphatase elevation noted in our phase II experience was related to this post procedural effect. The three patients who had significant elevation were ultimately found to have progressive disease on imaging which may have further contributed to this abnormality.

There is a growing body of evidence describing the benefit from DEBIRI use among patients with CRC liver metastases. Furthermore, this treatment approach is commonly used in clinical practice despite the limited data in the literature. Our phase II experience, however, raises a concern for tolerability of this regimen among heavily pre-treated metastatic colorectal patients. There is also lack of data regarding the maximum tolerated dose (MTD) of DEBIRI among this patient population and the toxicity profile and significance of liver function tests abnormalities among these patients are not known. We therefore propose this phase I study to evaluate the tolerability and safety of DEBIRI among patients with refractory metastatic colorectal cancer. In this study, in addition to escalating the dose of irinotecan, we will be using

a smaller size bead in an attempt to improve tolerability. In lieu of the experience of Martin et al., we will limit study treatment to two doses per lobe.

1.5 The Agent – Irinotecan:

Irinotecan is a well-known drug widely used as a systemic chemotherapeutic agent in gastro-intestinal malignancies. It is a derivative of the topoisomerase – 1 inhibitor class and exerts its cytotoxic effect by binding to topoisomerase – 1 DNA complex and inhibiting DNA repair [49]. It is approximately 50% protein bound in the circulation, undergoes non – cytochrome P450 hepatic metabolism and is excreted mainly via the biliary route and 20% renally. It has an elimination half-life of 6 to 12 hours. Common major side effects seen are nausea, vomiting, diarrhea, loss of appetite, myelosuppression, worsening hepatic function and hair loss.

Limited data are available regarding the pharmacokinetics of DEBIRI. Previous studies have shown a better toxicity profile compared to systemic irinotecan, with the main adverse event of post embolization syndrome (45). Recent data from Martin et al. reported some pharmcokinetics of the drug showing only minimally detectable levels of plasma irinotecan and its active metabolite SN-38 after up to 3 DEBIRI treatments in chemotherapy naïve patients with hepatic metastases from colorectal cancer. Each DEBIRI treatment involved administration of 100mg irinotecan loaded onto 100-300 μm beads and delivered via the hepatic artery (49). Our previous experience demonstrated increased alkaline phosphatase with use of the 100mg dose of DEBIRI among heavily treated patients. It is possible that this patient population is less amenable to intrahepatic therapy. Alternatively the use of larger bead size may contribute to the poor tolerance. Since refractory patients are often referred for these treatments due to limited treatment options, it is important to identify the MTD for this drug in this patient population. In the proposed phase I study we will use a smaller bead size and carefully escalate the irinotecan dose. These smaller beads are thought to result in better tumor penetration and drug delivery with less embolic effect. We will initiate treatment at 50mg of DEBIRI and escalate by 25mg with every subsequent treatment cohort until the MTD is reached. Cohort expansion will be planned at the MTD. Data from this trial will be used for development of future clinical trials utilizing DEBIRI among patients with refractory disease.

2.0 Objectives

2.1 Primary Objectives

To determine the maximum tolerated dose of drug eluting irinotecan beads, delivered intrahepatically for the treatment of liver only or liver-predominantly colorectal metastatic disease.

2.2 Secondary Objectives

To determine the response rate of colorectal liver metastases treated with drug- eluting irinotecan beads in refractory metastatic colorectal patients with liver only or liver predominant disease.

1. To determine the time to progression of colorectal liver metastases treated with drug-eluting irinotecan beads in refractory metastatic colorectal patients with liver only or liver predominant disease.

2. To determine the overall survival of patients treated with drug-eluting irinotecan beads for liver only or liver predominant metastatic disease from colorectal cancer.

3.0 Patient selection

3.1 Inclusion

3.1.1 Patients must be 18 years or older.

3.1.2 Patients must have a histologically or cytologically confirmed adenocarcinoma of the colon or rectum that is metastatic to the liver and unresectable and for which standard curative measures do not exist or are no longer effective.

3.1.3 Patients must have received prior fluoropyrimidine, oxaliplatin and irinotecan-based therapy for their disease and had progression or intolerance to these agents that resulted in treatment discontinuation.

3.1.4 Liver disease must not be amenable to potentially curative surgical resection.

3.1.5 Patients must have liver-only or liver-predominant disease to be eligible for this study. Liver predominant disease is defined dominant metastatic burden in the liver, with extra-hepatic disease that is judged by the investigator as unlikely to be life threatening within 3 months.

3.1.6 Patients must have a patent portal vein as documented by CT, MRI, or ultrasound.

3.1.7 Prior radiation therapy is allowed but must have been completed ≥4 weeks prior to study entry. Patients with history of prior radiation to the liver including radio-labeled microspheres cannot take part in this study.

3.1.8 Eastern Cooperative Oncology Group performance status 0 or 1.

3.1.9 Previous surgery or RFA to the liver is allowed. Patients with history of chemoembolization or radio-labeled microspheres are excluded.

3.1.10 Life expectancy of ≥12 weeks.

3.1.11 Patients must have organ and marrow function as defined below:

Leukocytes	≥ 3,000/µL
Absolute Neutrophil Count	≥1,500/µL
Platelets	≥ 100,000/µL
Total Bilirubin	≤1.5X ULN
AST(SGOT)/ALT(SGPT)	≤2 X ULN
Alkaline Phosphatase	≤2 X ULN
Creatinine	≤2.0 X mg/dL
PT/PTT	≤1.5 X ULN

3.1.12 Chemotherapy is harmful to the human fetus. For this reason, women of childbearing potential (WOCBP) and sexually active males must agree to use an accepted and effective method of contraception prior to study entry and for the duration of the study. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal. Women who use oral, implanted or injectable contraceptive hormones, or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy) should be considered to be of child bearing potential.

3.1.13 Patients must demonstrate ability to understand and the willingness to sign a written informed

consent document.

3.1.14 Patients must discontinue any medication that causes strong CYP3A4 induction 2 weeks prior to treatment initiation. Patients who are not able to discontinue these drugs are considered ineligible.

3.1.15 Patients must discontinue any medication that causes a strong CYP3A4 inhibition 1 week prior to treatment initiation. Patient who are not able to discontinue these drugs are considered ineligible.

3.2 Exclusion

3.2.1 Patients who have had chemotherapy (including targeted therapy i.e. cetuximab, panitumumab) or radiotherapy ≤ 4 weeks or treatment with bevacizumab ≤6 weeks prior to entering the study or those who have not recovered from acute adverse events due to agents administered more than 4 weeks earlier, with the exclusion of alopecia or neuropathy. Patients with history of radiation to the liver including radio-labeled microspheres at any point in their past will be excluded.

3.2.2 Patients may not be receiving nor have received any other investigational agent ≤ 4 weeks prior to study registration.

3.2.3 Pregnant or nursing women may not participate in this trial because of the increased risk of fetal harm including death from the therapeutic agents.

3.2.4 Patients with known brain metastases are excluded from this study because of their poor prognosis and frequent development of progressive neurological dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.5 Any patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, known HIV-positive patients and those with known hepatitis B or C are excluded from the study.

3.2.6 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active bacterial infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Patients with clinically evident ascites requiring medical management or paracentesis, or Childs-Pugh score B/C are not eligible.

3.2.8 Patients with evidence of other cancer within 5 years, excluding adequately treated basal cell carcinoma or squamous cell carcinoma of the skin.

3.2.9 Patient with significant cardiac, renal or hematologic or pulmonary dysfunction.

3.2.10 Patients with previous chemoembolization to liver metastases.

3.3 Pregnancy

The effects of DEBIRI on the developing human fetus at the recommended therapeutic dose are unknown. Women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of treatment, and for at least 3 months after the completion of treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Prior to study enrollment, WOBCP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In additional, men enrolled on this study should understand the risks to any sexual partner of childbearing potential.

All WOCBP must have a negative pregnancy test within ***72 hours*** prior to receiving the first dose of the investigational agent(s). If the pregnancy test is positive, the patient must not receive protocol treatment and must not be enrolled in the study.

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea $\geq$ 12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP.

3.4 Patient Registration

Eligible participants will be entered on study centrally by the Fox Chase Cancer Center QA Coordinator or their designee. Following registration, participants must begin protocol treatment within 14 days of registration. Issues that would cause treatment delays must be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled.

Participants may be registered from 9:00 am to 5:00 pm excluding holidays by calling the QA Coordinator at 215-728-4770. The site's investigator or designee will then fax or email the completed registration form, consent and HIPAA signature pages and eligibility checklist to 215-214-1511. The QA Coordinator or designee will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number assigned by the QA Coordinator prior to the initiation of treatment.

4.0 Treatment plan

This will be a single-center phase I study of DEBIRI for the treatment of metastatic colorectal cancer with liver only or liver predominant metastases. Treatment will be given in the interventional radiology department. All patients will be hospitalized for observation following DEBIRI treatment. Reported adverse events and potential risks of these agents and appropriate dose modifications are described in Section 5.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The following criteria for recovery of all toxicities must be documented prior to any additional DEBIRI treatments.

- Non-hematologic toxicities related to prior DEBIRI therapy must recover to ≤ grade 1 prior to any additional treatment.
- Alkaline phosphatase/ AST/ALT level must recover to ≤ grade 1 (less than 2.5 the upper limit of normal).
- Bilirubin elevation must recover to ≤ grade 1 (less than 1.5 the upper limit of normal)
- Neutropenia and thrombocytopenia must recover to ≤ grade 1 prior to any additional treatment

4.1 DEBIRI dose:

This will be a typical phase I study design of 3+3. The first cohort of patients will receive a dose of 50 mg of irinotecan per DEBIRI treatment. We will escalate by 25 mg with subsequent cohorts up to a dose of 100 mg of irinotecan per DEBIRI treatment (section 4.3).

Table 2: **Dose Escalation Schedule**

Dose Level	**Dose of Irinotecan in beads**
Level 1	50 mg per dose
Level 2	75 mg per dose
Level 3	100 mg per dose

At each dose level patients will be treated based on the presence of unilobar or bilobar disease and treated as described below.

4.1.1 Patients with unilobar disease

At each dose level the involved lobe will be treated twice with the appropriate dose of DEBIRI once every 3 weeks. CT scan for evaluation of response will be performed at 8 weeks. Further treatment is at the discretion of the treating physician.

4.1.2 Patients with bi-lobar disease

At each dose level the dominant lobe will be treated with the appropriate dose of DEBIRI for two treatments 3 weeks apart. CT images of the liver will be used to determine which lobe has the highest number or the largest lesions, and will be considered the dominant lobe. The response will be evaluated with CT at 8 weeks. In the absence of evidence of progression in the treated lobe (dominant lobe), 2 additional treatments can be administered to the untreated (non-dominant) lobe, at the same dose level. Repeat CT scan will be performed at 16 weeks. Further treatment is at the discretion of the treating physician.

- Treatment considerations
- Prior to each subsequent therapy patients will have all their blood work reviewed, to assure that they fill the eligibility criteria set forth for the study in section 3.1.11.
- Treatment may be delayed up to 2 additional weeks for labs to recover
- Failure to recover after 2 additional weeks will result in patient removal from the study
- Evaluating Response
- For purposes of planning follow-up treatments and measuring response, response will be defined by RECIST criteria for the treated lobe only.

- Progression of extra-hepatic metastases or progression in the untreated lobe will not be considered progression for the purposes of this trial. However, in these cases the patient and his treating physician may elect to terminate participation in this study.

- Response rate in treated liver lesion will be classified using RECIST criteria as outlined in section 8.0.

4.2 Technique for delivering DEBIRI

The following procedures will be followed for each treatment:

Pre-treatment: The patient should be kept NPO overnight prior to the treatment. Patients will be adequately pre-medicated as per the treating physician recommendation. In addition they will receive hydration, analgesics, antiemetics and prophylactic antibiotic therapy at the discretion of the physician performing the procedure. Diabetic patients on treatment with drugs from the Biguanides family (i.e. Metformin) will be required to discontinue their drug 24hr prior to the procedure and 2 days following the procedure. Diabetic patients and patients with creatinine 1.5-2.0 will receive aggressive hydration prior to the DEBIRI procedure. (See pre-admission order appendix A)

Pain Management: In prior studies of chemoembolization with LC Bead loaded with irinotecan, all patients reported moderate post procedural pain. Post procedure pain should be treated with parenteral narcotics under the discretion of the treating physician. Intra-arterial lidocaine (2-4cc) prior to injection of loaded beads may be used.

Chemoembolization with DEBIRI equipment: Patients will receive chemoembolization using LC Bead loaded with irinotecan. The beads used in this study will be the smallest size of 70-150µm (nominal). The beads will be mixed with a non-ionic contrast media in the vial immediately prior to use according to the instructions for use. Irinotecan will be loaded onto the beads not more than 2 hours prior to the procedure. The minimal incubation time is 2 hours for 98% absorption, but may be up to 5 hours for 100% absorption. Standard loading techniques and incubation time recommended by the sponsor will be used for all dose levels to ensure complete loading of the drug onto the beads (outlined in section 6.0). The study goal will be to deliver the full dose of irinotecan per treatment at each dose level. However, inherent factors such as arterial anatomy or other limiting procedural factors the dose may limit the total dose administered. Stasis in the target vascular bed is to be avoided, even if it means not delivering the entire intended dose.

Catheter Compatibility: The following catheter or an equivalent or larger French size catheter is compatible with the DEBIRI use.

Trade Name	**Manufacturer**	**Size**
Progreat™ Micro Catheter System	Terumo Corporation, 44-1, 2-Chome, Hatagaya, Shibuya-Ku, Tokyo 151-0072, Japan	2.4Fr Minimum outer diameter (O.D.) of 2.4Fr. (0.80mm) on the usable length of the catheter.

Procedure:
Using a unilateral femoral approach, selective catheterization of the hepatic artery will be performed. Vascular access is obtained via the common femoral artery and a guide-wire advanced under fluoroscopic

guidance. A micro- catheter is then inserted over the guide-wire. The superior mesenteric artery is selected and an angiogram performed to identify any aberrant arterial anatomy and verify antegrade portal vein flow. The celiac axis is then selected and an angiogram completed. The catheter and guide-wire are used to select the proper hepatic artery and a limited angiogram performed to identify the branches of the hepatic artery. The right or left hepatic artery is selected distal to the cystic artery (if visualized), depending on the location of the lesions to be treated.

Once the vascular supply of the tumor is identified, chemoembolization of the supplying artery is performed. At the discretion of the interventional radiologist, extra-hepatic vessels may be prophylactically embolized in order to mitigate risk of non-target deposition of DEBIRI. Patients with unifocal tumors will be treated with super selective chemoembolization. At the discretion of the investigator, a microcatheter may be used to select a second or third-order branch of the right or left hepatic artery in close proximity to the tumor.

Once the catheter is in place within the artery feeding the tumor, the LC Bead, loaded with irinotecan will be delivered into the artery. Radiological non-ionic contrast (preferably Omnipaque) will be used to guide the injection of beads. The beads will be mixed with contrast (according to the instructions for use) immediately prior to the procedure and injected slowly in 1ml aliquots using a 'sandwich technique' (i.e. beads then contrast) in order to identify and minimize reflux. Catheter selection will be by operator preference (e.g. the choice of a microcatheter, in case of tortuous, narrow or spastic vessels).

If vasospasm occurs, vasodilators may be given at the investigator's discretion. If the vasospasm does not resolve, the procedure should be aborted and the patient rescheduled. The catheter will then be removed and hemostasis achieved by manual compression or closure device. Each patient will be admitted for overnight care. The amount of contrast agent delivered to the patient during the procedure and dose of irradiation will be recorded as well as the time exposed to fluoroscopic imaging. All medications used during the procedure will be recorded, including pain management regime. The physician performing the procedure will grade the success of the procedure based on the following scale:

Grade	Lesion visualization/technical difficulty
0	Lesions not visualized, technically challenging procedure
1	Lesions sub-optimally visualized, procedure performed with some difficulty.
2	Lesions clearly visible, procedure performed without difficultly.

Post Treatment: Following the DEBIRI procedure all patients will be observed for vital signs, femoral access site, pain management and fluid hydration for about 24 hours. The procedure for pain management will be at the investigator's discretion. Blood for other labs, such as CBC or blood chemistries, may also be drawn on all patients prior to discharge. (See post treatment order from – appendix B).

Discharge: Upon discharge from the hospital, patients will be given a suitable pain management regimen based on normal hospital procedure. Written instructions for pain management will be given to patients according to their clinical need.

4.3 Definition of Dose-Limiting Toxicities

Definition: This will be defined as any of the following toxicities occurring during the 3 weeks following each DEBIRI treatment that are judged as possibly, probably, or definitely related to study agent:

- ≥ Grade 3 non-hematologic toxicity (excluding nausea, vomiting, or diarrhea responding to symptomatic management or LFTs)

- ≥ Grade 3 nausea, vomiting and diarrhea that has not responded to maximal medical symptomatic management after ≥ 72hr will be considered a DLT
- Grade 3 thrombocytopenia lasting > 5 days
- Grade 3 thrombocytopenia with ≥ grade 3 bleeding at any site
- Grade 4 thrombocytopenia
- Grade 4 neutropenia lasting > 5 days or associated with fever or infection
- Grade 3 alkaline phosphatase increase lasting more than 2 weeks post procedure
- Grade 4 alkaline phosphatase at any time
- Grade 3 ALT, AST and/or bilirubin elevation will be classified as a DLT based on the following criteria:
    - persistent AST/ALT elevation of 5-10 times the upper limit of normal for more than 2 weeks
    - Persistent AST/ALT elevation of >10-20 times the upper limit of normal for more than 1 week
- Grade 4 ALT, AST and/or bilirubin elevation at any time.

Dose escalation will proceed to the next cohort according to the following schema:

# of Patients with DLT at a Given Dose	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared to have exceeded the maximum tolerated dose Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. · If 0 of these 3 patients experience DLT, proceed to the next dose level. · If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared to have exceeded the maximum tolerated dose. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6	This is generally the MTD and recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

4.4 Supportive care guidelines

- Prophylactic use of granulocyte growth factors is not permitted. Use of these hematopoietic factors for grade 4 myelosuppression associated with infection or bleeding is permitted at the discretion of the treating physician and according to guidelines of the American Society of Clinical Oncology. Use of granulocyte growth factor support after neutropenic fever as a secondary prophylaxis is allowed per treating physician discretion.
- Use of erythropoietin is allowed at the discretion of the treating physician.
- Blood transfusions are allowed at the discretion of the treating physician.
- For management of treatment-related side effects, the use of standard supportive care including anti-emetics, intravenous hydration, and analgesics is strongly encouraged and will be decided upon by the treating physician.

4.5 Concomitant medications

- Patients may not receive any other anticancer therapy while on study, including immunotherapy. Patients may not receive any other clinical investigational drug.
- If nausea, vomiting, or diarrhea occurs, effective symptomatic treatment can be initiated. For diarrhea, loperamide (Imodium®) should be used as standard therapy.

4.6 Duration of therapy

Therapy will continue per protocol until any of the following conditions occur

- Disease progression in treated lobe.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse events.
- Patient decides to withdraw from study.
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator.
- Judgment of the treating physician that further therapy is unlikely to be of benefit to the patient

4.6.1 Patient withdrawal

Patients may be withdrawn from the study by the investigator or terminate their participation prematurely based on the following:

- Post-consent determination of ineligibility.
- Lack of therapeutic efficacy, as evidenced by progression of treated intra-hepatic disease (progression of untreated liver metastasis or extra-hepatic disease will not be considered failure of therapy). In the latter cases termination of the protocol will be determined according to section 8.1.2. For protocol purposes the patient will be classified based on the response rate of his treated liver lesions using RECIST criteria (as outlined in section 8.1).
- Interval down staging of target lesions such that the patient would be an acceptable candidate for surgical resection.
- Physician's judgment following an adverse event or unacceptable toxicity.
- Termination by the Sponsor, or a regulatory authority.
- Patients that require radiation therapy for local palliative purposes.

Any other reason for withdrawal that the treating physician or patient indicates is in the overall best interest of the patient.

4.7 Follow Up

The patient will be clinically evaluated approximately 30 days after completion of the trial. Telephone follow up at 3 month intervals for up to 2 years for survival and toxicity monitoring will be conducted. At treating physician discretion, patients may be followed more frequently for toxicities felt to be treatment-related.

5.0 Adverse Events

5.1 Definitions

5.1.1 Adverse Events (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*.

5.1.2 Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

5.1.3 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

5.1.4 Attribution/Relationship to study drug

1. Definite – clearly related
2. Probable – likely related
3. Possible – may be related
4. Unlikely – doubtfully related
5. Unrelated – clearly not related

5.1.5 Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent

document, and (b) other relevant sources of information, such as product labeling and package inserts:

OR

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.(OHRP Guidance on reviewing unanticipated problems 2007)

5.2 Recording and Reporting Responsibilities

5.2.1 Investigative site recording responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

3. All SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports should the event require further investigation.

5.2.2 Investigative site reporting responsibilities:

1. The investigator/ site is responsible to report all SAEs that occur on or after the first day of study treatment and up to 30 days after the last study treatment to the Sponsor within 24 hours of becoming aware of the event.

2. Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by email to SAE.FCCC@fccc.edu.

3. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the OCR, draft revisions will be made in track changes and submitted to the OCR for consideration. Any consent revisions must receive OCR approval **prior** to submission to the IRB.

4. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call Study Monitor for confirmation with the Sponsor-Investigator.

5. If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

6. Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in the trial master file.

Participating sites should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

5.2.3 Sponsor Reporting Responsibilities:

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
   i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
   ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
   iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the ISRU for each site's IRB of record along with the report of the adverse event.

3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study within the OCR.

4. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines (http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

   Food and Drug Administration (FDA)
   Center for Devices and Radiological Health
   Document Mail Center – W066-G609
   10903 New Hampshire Avenue
   Silver Spring, MD 20993-0002

   In addition, any Medical Device Report (MDR) may be faxed to FDA following approval. A request for approval of facsimile reports can be obtained by calling 301-827-7537

   AND

Within 24 hours of becoming aware:

Biocompatibles Inc., a BTG International Group Company
pharmacovigilance@btgplc.com

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported.

6.0 DEBIRI formulation and procurement

LC Bead microspheres are produced from a biocompatible polyvinyl alcohol (PVA) hydrogel that contains sulphonate groups which allow the controlled loading and delivery of chemotherapeutic drugs. LC Bead occludes the blood flow to the target tissue and delivers a local and sustained dose of drug direct to the tumor. LC bead is 510K cleared by the FDA for the embolization of hypervascularized tumors and arteriovenous malformations (AVMs) only. Loading of irinotecan into the LC Bead is considered investigational in the US.

LC Bead is biochemically identical to DC Bead which received CE mark approval in 2003 and is indicated for the treatment of malignant hyper-vascularised tumors and loading with doxorubicin. DC Bead may also be loaded with Irinotecan for the treatment of metastatic colorectal cancer.

The intention of this study is to use LC Bead loaded with irinotecan for the purpose of: embolization of vessels supplying malignant metastatic tumor(s) and delivery of a local, controlled, sustained dose of irinotecan to the tumor(s)

LC Bead comprise a range of hydrogel microspheres that are biocompatible, hydrophilic, non resorbable and precisely calibrated. Various beads sizes are available for use ranging from 70 to 900μm. In this study we will utilize the smallest size beads (70-150 μm- Yellow-black label – M1), which are thought to have improved penetration to the tumor and therefore more targeted drug delivery.

Upon loading with irinotecan, LC Bead undergo a slight decrease in size, up to 30% when loading at 50mg/ml. At the time of use, LC Bead will be mixed with irinotecan according to the instructions for loading. LC Beads are suitable for loading irinotecan Solution (20mg/ml) ONLY. With the use of M1 LC beads it is recommended that the user will ensure that the size is appropriate for the intended vasculature. In addition, patients should be carefully monitored for signs of non-target embolization such as hypoxia or CNS changes. Finally the user should consider upsizing of the beads if angiographic evidence of embolization does not appear quickly during delivery.

Drug loading instructions: These are the loading instruction for all dose levels on this study.

1. Remove as much saline as possible from a vial of LC Bead using a syringe with a small gauge needle.
2. Using a syringe and needle add the appropriate amount of Irinotecan solution (solution concentration of 20mg/ml) directly to the vial of LC Bead, as outlined in the table below:

Irinotecan dose	Amount to be added to LC beads
50mg	2.5ml
75mg	3.75ml
100mg	5ml

3. Agitate the LC Bead / Irinotecan solution gently to encourage mixing then allow standing. The beads will turn a turquoise color as the loading progresses.
4. The minimal incubation time is 2 hours for 98% absorption, but may be up to 5 hours for 100% absorption.
5. Prior to use, transfer the LC Bead loaded with irinotecan to a syringe and expel the excess supernatant using a filter needle. Add 5ml sterile water, in order to minimize irinotecan elution, and add 10-20 cc of contrast media per 1ml/cc of irinotecan loaded beads. Invert the syringe gently to obtain an even suspension of DC Bead.

LC Bead loaded with irinotecan is physically and chemically stable for up to 14 days if stored in a fridge at 2-8°C or 4 hours at room temperature in the absence of non-ionic contrast media. However the allocation of a shelf-life longer than 4 hours at room temperature or 24 hours if stored in the fridge is the responsibility of the user and dependent upon the use of controlled aseptic conditions for preparation. The irinotecan loaded bead solution will be mixed with non-ionic contrast only at the time of injection into the patient via a properly placed catheter or microcatheter.

In this protocol the beads will be loaded within 2 hours of the procedure. Discard any unused LC Bead loaded with irinotecan.

7.0 Study Calendar

All pre-study/baseline evaluations except serum pregnancy test may be performed up to 28 days prior to registration. A timetable of relevant assessments is provided in the table below for uni-lobar and bi-lobar disease (all tests can be performed within ±2 days of this schedule). This timetable contains the schedule for two treatments 3 weeks apart followed by CT on week 8. The schedule can be repeated for additional treatment in appropriate cases (section 4.2.1).

Based on experience from previous studies using DEBIRI there exists a risk of post procedure transient edema, which may confound the response evaluation by RECIST criteria. In case of disease progression on week 8 imaging the patient will be followed with repeat CT at 12 weeks to rule out the possibility of edema accounting for the progressive disease.

Study Calendar

	Pre-Study	Day 1 (± 2)[i]	Day 2[i]	Day 8	Day 15	Day 22 (± 2)[i]	Day 23[i]	Day 29	Day 36	Day 57	EOT[h]	Follow Up for Survival[j]
Planned treatment (Unilobar/dominant lesion in bilobar disease) ± 2 days[a]		X				X						
Informed consent	X											
Demographics	X											
Medical History[b]	X											
Concurrent meds	X	X----------X										
Physical exam[b]	X		X	X	X	X	X	X	X		X	
Height	X											
Performance Status	X					X					X	
CBC w/diff[c]	X		X	X	X	X	X	X	X		X	
Serum chemistry[c]	X		X	X	X	X	X	X	X		X	
CEA[d]	X									X	X	
PT/INR/PTT[e]	X					X					X	
Adverse Event Evaluations		X----------X										
CT scan of the chest abdomen & pelvis[f]	X									X[K]		
B-HCG[g]	X											
Hepatic angiogram		X										

a. Patients with unilobar disease will be treated on day 1 ± 2 days and 3 weeks later on day 22 ± 2 days with CT 8 weeks after the initial treatment. Patient with bilobar disease will receive treatment to the dominant lobe on day 1 ± 2 days and 3 weeks later on day 21 ± 2 days with CT 8 weeks after the initial treatment. Patients without evidence of progression will be candidates for treatment of the non-treated lobe for 2 treatments 3 weeks apart.

b. Medical history and physical examination will be obtained prior to each treatment according to the treatment schedule (±2 days). Pre-treatment medical history can consist of interval history.

c. CBC and Chemistry are to be obtained on the day before treatment (±2 days), and every week while on the study (±2 days). Additional blood tests should be performed per the discretion of the treating physician. Blood work obtained within ±2 days may be used.

d. CEA evaluation will be obtained at the beginning of the study and with each imaging evaluation.

e. PT/INR/PTT only required prior to each procedure.

f. Additional imaging may be obtained at discretion of treating physician (e.g. MRI, PET scan, etc.). Alternative imaging of liver (ie MRI in place of CT scan) is acceptable when preferred by treating physician. MRI of the liver may be used as a substitute for a CT scan for patients with creatinine 1.5-2.0 who are at risk for contrast induced nephropathy. Diabetic patients treated with medications from the biguanides family such as Metformin would be required to hold their medicine for 1 day before and 2 days after their scheduled CT scan.

g. Serum pregnancy test (women of childbearing potential) within 72 hours before treatment.

h. Off-study evaluation. Two consecutive measurements taken at least 4 weeks apart must be used to document partial or complete responses in patients meeting these criteria with measurable disease. Follow-up details are available in section 4.7.

i. Following the procedure the patient will be admitted for overnight observation. On day 1 post treatment blood work including CBC and CMP will be obtained along with physical examination.

j. Patients will be followed up for overall survival status. Medical evaluation is NOT required to determine status. The patient will be clinically evaluated approximately 30 days after completion of the trial. Telephone follow up at 3 month intervals for up to 2 years for survival and toxicity monitoring will be conducted. At treating physician discretion, patients may be followed more frequently for toxicities felt to be treatment-related.

k. Patients who demonstrate progression with their Day 57 (week 8) CT scan should have a repeat CT scan at week 12 to rule out inflammation as a source of tumor enlargement.

8.0 Measurement of Effect

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, all patients will be evaluated for response 8 weeks following the administration of DEBIRI, response rate will be calculated based on the treated lobe only. In addition to a baseline scan, confirmatory scans must be obtained at least 4 weeks following the initial documentation of complete or partial response. In cases of disease progression at 8 weeks, repeat CT will be done at 12 weeks to exclude the possibility of treatment related transient edema accounting for disease progression.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1 (50, 51) . RECIST 1.1 limits the number of measurable lesions in an organ to 2 and the total number of measurable lesions to 5. Since response is being evaluated in this study only in the treated lobe of the liver, we will measure response on up to 5 total lesions in that lobe of liver.

Patients must have at least one measurable lesion, defined as >20mm using CT or MRI, or >10mm using spiral CT. Where disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology/histology.

Baseline measurements must be taken not more than four weeks prior to commencement of treatment. The same measurement technique (CT/MRI) must be used at baseline and follow up. No more than 5 target lesions in the liver will be identified. Those with the largest diameters should be included.

A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. Change on the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy.

8.1 Response Criteria

8.1.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions, or disappearance of arterial enhancement in the target lesion
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	1. At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started. 2. The appearance of one or more new lesions. 3. Death due to disease without objective evidence of progression

Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Symptomatic Deterioration	Is defined as a global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.
In evaluable for Response	Is defined as having no repeat tumor assessments following initiation of study therapy for reasons unrelated to symptoms or signs of disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion (51).
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

8.1.2 Progressive disease outside of the liver:

For protocol purposes new or increasing lesions outside of the liver will not be considered progressive disease. However, the protocol will be discontinued in the following cases in which the extent of disease limits further benefit of liver-directed treatment:

- Diffuse pulmonary disease
- Diffuse peritoneal carcinomatosis
- Diffuse lymph node involvement
- Diffuse bone metastases with bone marrow compromise
- New metastatic disease resulting in organ dysfunction, or intractable pain.

The treating physician may elect to terminate participation in this protocol in other cases in which alternative therapy is indicated.

8.2 Duration of response

For purposes of this study, response rate will be calculated based on the treated lobe only.

Overall response: The duration of overall response is measured from the time measurement

criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.3 Time to progression

Time to progression (TTP) is defined as the duration of time from start of treatment to progression in the treated lobe.

9.0 Statistical Considerations:

The study is a phase I study with a total of 3 dose levels. For the dose-escalation portion of the study, approximately 9 evaluable subjects will be required if DLTs do not occur (3 subjects in each of the dose cohorts, 50, 75, 100). If a DLT does occur among the first 3 subjects in a cohort, 3 additional subjects will be added to the cohort. In case 2 or more DLTs occur in a cohort, a total of 6 subjects will be treated at the preceding dose, which will be evaluated for MTD. At a minimum we will enroll 3 patients at each dose level with an expansion of the last dose level with 14 additional patients. Therefore we are estimating accrual of 9-30 patients under this protocol. For each dose-escalation arm during Phase 1 the evaluable population for DLT includes all subjects enrolled in the dose-escalation arm, who received at least 1 full cycle of DEBIRI. The Safety Population includes all subjects who receive treatment with DEBIRI.

At the dose expansion level 10% of DLT will be acceptable and 33% will be unacceptable. We would terminate the study if ever 4 DLTs occur including 1 that would have occurred in the MTD cohort of 6 patients. The chance of declaring the treatment too toxic when only 10% toxic is about 9% while the chance of this decision when the true toxicity id 33% is about 85%.

Reporting and Exclusions

9.1.1 Evaluation of toxicity.

All patients will be evaluable for toxicity from the time of their first treatment with DEBIRI until study completion. Toxicity reports will be carried out as detailed in section 5.0.

9.1.2 Evaluation of response.

All patients with measurable disease included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories:
1) Complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). (47)

9.2 Data Safety Monitoring Plan

9.2.1 Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the study Sponsor-Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and Sponsor-Investigator as applicable.

9.2.2 Data & Safety Monitoring Committee

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed at least every 6 months by the Fox Chase Cancer Center Data Safety Monitoring Board (FCCC DSMB). In this capacity the FCCC DSMB will serve as an advisory committee to the Sponsor-Investigator. The FCCC DSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Study Sponsor-Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Sponsor-Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

10.0 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

10.1 Data Reporting

The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit.

The ISRU is responsible for compiling and submitting data to the Sponsor-Investigator and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Data and Safety Monitoring Board.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The ISRU is responsible for distributing and tracking review of all IND/IDE Action Letters, Safety Reports, study specific Serious Adverse Events

10.2 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the OCR and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the Study Monitor must be notified

of any plans to move records to an offsite location prior to doing so.

10.3 Study Agents

Any study agent supplied through the OCR from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

10.4 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file according to site policy.

Appendix A – Pre-treatment orders:

1. **Ancef 1 gram IVPB (If PCN allergy use Vancomycin 500mg IVPB)**
2. **Flagyl 500mg IVPB**
3. **Benadryl 50mg IVP**
4. **Decadron 10mg IVP (can be omitted if patient is diabetic, at the discretion of the treating physician)**
5. **Zofran 8mg IVP.**
6. **Normal saline 100cc/hr IV. Patients with creatinine 1.5-2.0 should receive an additional bolus of 1000ml normal saline IV prior to the procedure.**
7. **Sedation: Fentanyl and Versed for conscious sedation.**
8. **If the patient is diabetic receiving therapy with drugs from the Biguanides family (i.e. Metformin), the physician should verify that the patient has been off the drug for 1 day prior to the procedure.**

Appendix B– Post-treatment order form:

Admit to medicine for overnight observation following procedure.

1. **Bed rest from_____to_____.**
2. **Elevation of the head of the bed by 10 degrees each hour up to 30 degrees.**
3. **Monitor for hematoma and pulse at the puncture site with vital signs q15min for the first hour; every 30 min for the following 2 hours; every 1 hour for the next 3 hours.**
4. **Apply direct pressure in the presence of expanding hematoma and contact treating interventional radiologist immediately.**
5. **Call treating interventional radiologist immediately for loss of pulse or new or increasing arterial insufficiency (coldness, blue discoloration, numbness, pain, tingling) in the extremity of the puncture site.**

Fluid:	**1000ml D51/2 NSS @ 125 cc/hr**
Anti-emetics	**Zofran 8mg IVP PRN for nausea**
Analgesics	**Dilaudid 1mg IV push Q 2H PRN for pain**
Labs – on the morning following procedure	**CBC** **CMP**

Discharge decision will be made by the treating interventional radiologist during admission. Clinically stable patients may be discharged home after 24hr observation and follow up as an outpatient for repeat blood work in 1 week.

For diabetic patients receiving therapy with drugs from the Biguanides family (i.e. Metformin) they should be instructed to hold the drug for 2 days following the procedure.

Appendix C - DEBIRI adverse event profile

Table 1: Articles reporting complications/adverse events in mCRC patients treated using DC Bead with Irinotecan

Table reproduced with permission from Biocompatibles UK Ltd
Source: Biocompatibles Embolic Agents - Adverse Events Analysis (REVISION 3) July 2011

Reference	Population	Number of Patients	No of Treatments
Fiorentini 2008	mCRC	20	35
Fiorentini 2009b	mCRC	20	40
Fiorentini 2009a	mCRC	35	72
Martin 2009b	mCRC Cholangiocarcinoma Other	109	187
Martin 2009d	mCRC	55	99
Martin 2009c	mCRC	30	57
Bower 2010	mCRC	55	90
CA1011	mCRC	11	40
Aliberti 2006	mCRC	10	18
Aliberti 2009	mCRC	82	185
Yadavali 2009	mCRC	24	28
O'Grady 2009	mCRC - resectable	7	7
Narayanan 2010	mCRC	16	26
	Total Number of Patients	**304**	**585**

Table X: Number of Complications reported in the literature and overall incidence for DC Bead and Irinotecan.
Table reproduced with permission from Biocompatibles UK Ltd
Source: Biocompatibles Embolic Agents - Adverse Events Analysis (REVISION 3) July 2011

Event	N (%)	Overall Incidence N (%)	Reference
Acute Pancreatitis	1/82 (1.2%) 1/20 (5%) 1/24 (4.2%)	3/304 (1.0%)	Aliberti 2009 Fiorentini 2008 Yadavali 2009
Alopecia	7/10 (70%)	7/304 (2.3%)	Aliberti 2006
Anaemia	1/55 (1.8%) 2/35 (5.7%)	3/304 (1%)	Martin 2009d Fiorentini 2009a
Anorexia	3/55 (5%) 1/16 (6%)	4/304 (1.3%)	Martin 2009d Narayanan 2010
Asthenia (G1-2)	8/10 (80%) 7/35 (20%) 1/11 (9.1%)	16/304 (5.3%)	Aliberti 2006 Fiorentini 2009a CA1011
Cholecystitis	1/55 (1.8%)	1/304 (0.3%)	Martin 2009d
Constipation	1/11 (9.1%)	1/304 (0.3%)	CA1011
Diarrhoea	1/35 (2.8%)	1/304 (0.3%)	Fiorentini 2009a
Dehydration	1/55 (1.8%)	1/304 (0.3%)	Martin 2009d
Dyspnoea	1/11 (18.1%)	1/304 (0.3%)	CA1011
Fatigue	1/16 (6%)	1/304 (0.3%)	Narayanan 2010
Gastritis	1/55 (1.8%)	1/304 (0.3%)	Martin 2009d
Hypertension	1/55 (1.8%) 1/11 (9.1%)	2/304 (0.7%)	Martin 2009d CA1011
Haematoma	1/7 (14%) 1/24 (4.2%)	2/304 (0.7%)	O'Grady 2009 Yadavali 2009

Infection	1/11 (9.1%)	1/304 (0.3%)	CA1011
Insomnia	1/16 (6%)	1/304 (0.3%)	Narayanan 2010
Leucopenia	2/35 (5.7%)	2/304 (0.7%)	Fiorentini 2009a
Liver Abscess	1/10 (10%)	2/304 (0.7%)	Aliberti 2006

Event	N (%)	Overall Incidence N (%)	Reference
	1/20 (5%)		Fiorentini 2008
Liver dysfunction/failure	4/55 (7.3%)	4/304 (1.3%)	Martin 2009d
Musculoskeletal chest pain	1/11 (9.1%)	1/304 (0.3%)	CA1011
Pain	2/11 (18.1%)	2/304 (0.7%)	CA1011
Palpitations	1/11 (9.1%)	1/304 (0.3%)	CA1011
Post Embolisation Syndrome URQP URQP (G2) (G3)	 10/10 (100%) 74/185* (40%) 10/20 (50%) 5/20 (25%)	99/304 (33%)	 Aliberti 2006 Aliberti 2009 Fiorentini 2008 Fiorentini 2008
Abdominal Pain	5/16 (31%) 11/35 (31%) 6/11 (55%)	22/304 (7.2%)	Narayanan 2010 Fiorentini 2009a CA1011
Fever (G2)	148/185* (80%) 20/20 (100%) 7/35 (20%)	175/304 (58%)	Aliberti 2009 Fiorentini 2008 Fiorentini 2009a
Nausea Nausea (G2) Nausea/Vomiting (G2)	5/99* (5%) 6/16 (37%) 6/11 (55%) 148/185* (80%) 20/20 (100%)	185/304 (61%)	Martin 2009d Narayanan 2010 CA1011 Aliberti 2009 Fiorentini 2007
Inc Transaminases (G2-3)	130/185* (70%)	130/304 (43%)	Aliberti 2009
PES (nausea/emesis)	1/11 (9%)	1/304 (0.3%)	Bower 2010
Pneumonia	1/55 (1.8)	1/304 (0.3%)	Martin 2009d
Vomiting	2/16 (12%) 1/7 (14%) 14/35 (40%) 8/10 (80%) 3/55 (5%) 7/11 (64%)	22/304 (7.2%)	Narayanan 2010 O'Grady 2009 Fiorentini 2009a Aliberti 2006 Martin 2009d CA1011
WBC Increase	1/11 (9.1%)	1/304 (0.3%)	CA1011
Transient Ischaemic Attack	1/24 (4.2%)	1/304 (0.3%)	Yadavali 2009

*Denominator is procedures not patients in these cases

Table 2: Overall incidence of complications relating to DC Bead and Irinotecan in mCRC – comparison with Events documented in the Baseline Risk Document for cTACE and systemic irinotecan

Table reproduced with permission from Biocompatibles UK Ltd

Source: Biocompatibles Embolic Agents - Adverse Events Analysis (REVISION 3) July 2012

Event	Overall N (%)	Baseline Risk N (%)	Reference
Anaemia	3/304 (1%)	2/26 (7.6%) 4.5% (G3-4)	Bavisotto 1999 Pfizer prescribing info 2008
Asthenia (G1-2)	16/304 (5.3%)	10/11 (91%) (G1-2) 69% (G1-2) 14% (G3-4)	Voigt 2002 Pfizer prescribing Info 2008
Constipation	1/304 (0.3%)	1/26 (3.8%) 32% (G1-2) 0.4% (G3-4)	Bavisotto 1999) Pfizer prescribing Info 2008
Diarrhoea	1/304 (0.3%)	1/11 (9%) 5/41 (12%) 9/50 (17%) 1/26 (3.8%) 83% (G1-2) 31% (G3-4)	Voigt 2002 Pajkos 1998 Salman 2002 Bavisotto 1999 Pfizer prescribing info 2008
Dyspnoea	1/304 (0.3%)	2/26 (7.6%) 22% (G1-2) 2.2% (G3-4)	Bavisotto 1999 Pfizer prescribing info 2008
Infection	1/304 (0.3%)	2/26 (7.6%) 14% (G1-2) 0.4% (G3-4)	Bavisotto 1999 Pfizer prescribing info 2008
Insomnia	1/304 (0.3%)	1/26 (3.8%) 19% (NCI G1-4)	Bavisotto 1999 Pfizer prescribing info 2008
Leucopenia	2/304 (0.7%)	2/41 (5%) 97% (G1-2) 22% (G3-4)	Pajkos 1998 Pfizer prescribing info 2008
Pneumonia	1/304 (0.3%)	1/26 (3.8%) 3.6% (G1-2) 1.3% (G3-4)	Bavisotto 1999 Pfizer prescribing info 2008

Table 3: Overall incidence of complications relating to DC Bead and Irinotecan in mCRC – comparison with Events documented in the Baseline Risk Document for cTACE and systemic irinotecan

Table reproduced with permission from Biocompatibles UK Ltd
Source: Biocompatibles Embolic Agents - Adverse Events Analysis (REVISION 3) July 2012

Event	Overall N (%)	Baseline Risk N (%)	Reference
Acute Pancreatitis	3/304 (1%)	(1.7-4%)	Ozcinar 2009
Cholecystitis	1/304 (0.3%)	1/21 (5%)	Wasser 2005
Fatigue	1/304 (0.3%)	"Common" in 40	Sanz-Altamira 1997
Gastritis	1/304 (0.3%)	3/26 (11.5%)	Bavisotto 1999
Haematoma	2/304 (0.7%)	1/54 (2%)	Swanson 2002
Liver Abscess	2/304 (0.7%)	9/3878 (<1%) 3/2012 (0.15%0 2/176 (1.1%) 1/278 (0.4%) 2/72 (2.7%)	Ong 2004 Xia 2006 Chen 1999 Kiely 2006 Farinati 1996
Liver dysfunction/failure	4/304 (1.3%)	2/102 (2%)	PV 2010
Post Embolisation Syndrome Abdominal Pain Fever Nausea Nausea/Vomiting	99/304 (33%) 22/304 (7.2%) 175/304 (58%) 185/304 (61%) 1/304 (0.3%)	(86%) 91/126 (72.2%)	Gd'ETCH 1995 Chabrot 2009
Inc Transaminases (G2-3)	130/304 (43%)	135/145(93%)	Wigmore 2003
WBC Increase	1/304 (0.3%)	Observed in TACE	Wagnetz 2010
Musculoskeletal chest pain	1/304 (0.3%)	Not documented	
Palpitations	1/304 (0.3%)	Not documented	
Hypertension	2/304 (0.7%)	Not documented	
Transient Ischaemic Attack	1/304 (0.3%)	Not documented	

References:

1. Venook AP, Stagg RJ, Lewis BJ, Chase JL, Ring EJ, Maroney TP, et al. Chemoembolization for hepatocellular carcinoma. J Clin Oncol. 1990;8(6):1108-14.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: a cancer journal for clinicians. 2012;62(1):10-29.
3. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. . J Clin Oncol. 1992;10:896-903.
4. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol. 2003;21(5):807-14.
5. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet. 1998;352(9138):1413-8.
6. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-42.
7. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658-64.
8. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757-65.
9. Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(14):2311-9.
10. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol. 2008;26(21):3523-9.
11. Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Annals of surgery. 2000;231(4):487-99.
12. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. Surgery. 1974;75(4):589-96.
13. Anand A, Anand N. Re: Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst. 1996;88(12):838-9.
14. Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481).

J Clin Oncol. 2006;24(9):1395-403.

15. Kemeny N, Jarnagin W, Paty P, Gonen M, Schwartz L, Morse M, et al. Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. J Clin Oncol. 2005;23(22):4888-96.

16. Ducreux M, Ychou M, Laplanche A, Gamelin E, Lasser P, Husseini F, et al. Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. J Clin Oncol. 2005;23(22):4881-7.

17. Kemeny N, Jarnagin W, Gonen M, Stockman J, Blumgart L, Sperber D, et al. Phase I/II study of hepatic arterial therapy with floxuridine and dexamethasone in combination with intravenous irinotecan as adjuvant treatment after resection of hepatic metastases from colorectal cancer. J Clin Oncol. 2003;21(17):3303-9.

18. Gallagher DJ, Capanu M, Raggio G, Kemeny N. Hepatic arterial infusion plus systemic irinotecan in patients with unresectable hepatic metastases from colorectal cancer previously treated with systemic oxaliplatin: a retrospective analysis. Ann Oncol. 2007;18(12):1995-9.

19. Evans J. Ablative and catheter-delivered therapies for colorectal liver metastases (CRLM). Eur J Surg Oncol. 2007;33 Suppl 2:S64-75.

20. Stuart K. Chemoembolization in the management of liver tumors. Oncologist. 2003;8(5):425-37.

21. Lang EK, Brown CL, Jr. Colorectal metastases to the liver: selective chemoembolization. Radiology. 1993;189(2):417-22.

22. Martinelli DJ, Wadler S, Bakal CW, Cynamon J, Rozenblit A, Haynes H, et al. Utility of embolization or chemoembolization as second-line treatment in patients with advanced or recurrent colorectal carcinoma. Cancer. 1994;74(6):1706-12.

23. Hunt TM, Flowerdew AD, Birch SJ, Williams JD, Mullee MA, Taylor I. Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases. Br J Surg. 1990;77(7):779-82.

24. Borner M, Castiglione M, Triller J, Baer HU, Soucek M, Blumgart L, et al. Considerable side effects of chemoembolization for colorectal carcinoma metastatic to the liver. Ann Oncol. 1992;3(2):113-5.

25. Lorenz M, Herrmann G, Kirkowa-Reimann M, Rauber K, Herrhausen T, Henne T, et al. Temporary chemoembolization of colorectal liver metastases with degradable starch microspheres. Eur J Surg Oncol. 1989;15(5):453-62.

26. Tellez C, Benson AB, 3rd, Lyster MT, Talamonti M, Shaw J, Braun MA, et al. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of the literature. Cancer. 1998;82(7):1250-9.

27. Salman HS, Cynamon J, Jagust M, Bakal C, Rozenblit A, Kaleya R, et al. Randomized phase II trial of embolization therapy versus chemoembolization therapy in previously treated patients with colorectal carcinoma metastatic to the liver. Clin Colorectal Cancer. 2002;2(3):173-9.

28. Lewis AL, Gonzalez MV, Lloyd AW, Hall B, Tang Y, Willis SL, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol. 2006;17(2 Pt 1):335-42.
29. Taylor RR, Tang Y, Gonzalez MV, Stratford PW, Lewis AL. Irinotecan drug eluting beads for use in chemoembolization: in vitro and in vivo evaluation of drug release properties. Eur J Pharm Sci. 2007;30(1):7-14.
30. Poon RT, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol. 2007;5(9):1100-8.
31. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46(3):474-81.
32. Malagari K, Chatzimichael K, Alexopoulou E, Kelekis A, Hall B, Dourakis S, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol. 2008;31(2):269-80.
33. Malagari K, Alexopoulou E, Chatzimichail K, Hall B, Koskinas J, Ryan S, et al. Transcatheter chemoembolization in the treatment of HCC in patients not eligible for curative treatments: midterm results of doxorubicin-loaded DC bead. Abdom Imaging. 2008;33(5):512-9.
34. Lencioni R, Crocetti L, Petruzzi P, Vignali C, Bozzi E, Della Pina C, et al. Doxorubicin-eluting bead-enhanced radiofrequency ablation of hepatocellular carcinoma: a pilot clinical study. J Hepatol. 2008;49(2):217-22.
35. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33(1):41-52.
36. Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Kim HS. Drug eluting beads versus conventional TACE for unresectable hepatocellular carcinoma: Survival benefits and safety. J Clin Oncol. 2009 27:15s:suppl; abstr 4524.
37. van Malenstein H, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie. 2011;34(7):368-76.
38. Song MJ, Chun HJ, Song DS, Kim HY, Yoo SH, Park CH, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. Journal of hepatology. 2012.
39. Eyol E, Boleij A, Taylor RR, Lewis AL, Berger MR. Chemoembolisation of rat colorectal liver metastases with drug eluting beads loaded with irinotecan or doxorubicin. Clin Exp Metastasis. 2008;25(3):273-82.
40. Tang Y, Czuczman PR, Chung ST, Lewis AL. Preservation of the active lactone form of irinotecan using drug eluting beads for the treatment of colorectal cancer metastases. J Control Release. 2008;127(1):70-8.
41. Aliberti C, Tilli M, Benea G, Fiorentini G. Trans-arterial chemoembolization

(TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: preliminary results. Anticancer Res. 2006;26(5B):3793-5.
42. Martin R, Robbins K, Metzger T, O'Hara R, Bosnjakovic P, Tomalty D. Hepatic intra-arterial injection of irinotecan eluting beads in unresectable colorectal liver metastatic refractory to standard systemic chemotherapy: Results of multi-institutional study. 2009 Gastrointestinal Cancers Symposium
Abstract # 185.
43. Fiorentini G, Aliberti C, Turrisi G, Del Conte A, Rossi S, Benea G, et al. Intraarterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase II clinical study. In Vivo. 2007;21(6):1085-91.
44. Aliberti C, Benea A, Tilli G, Fiorentini G. Transarterial chemoembolization (TACE) of liver metastases (LM) from colorectal carcinoma (CRC) adopting drug eluting beads preloaded with irinotecan (DEBIRI): Results of a phase II study on 82 patients. J Clin Oncol 2009;27:15s(suppl; abstr 4092).
45. Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32(4):1387-95.
46. Martin RC, Joshi J, Robbins K, Tomalty D, O'Hara R, Tatum C. Transarterial Chemoembolization of Metastatic Colorectal Carcinoma with Drug-Eluting Beads, Irinotecan (DEBIRI): Multi-Institutional Registry. J Oncol. 2009;2009:539795. PMCID: 2771155.
47. Martin RC, Joshi J, Robbins K, Tomalty D, Bosnjakovik P, Derner M, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi- institutional study. Ann Surg Oncol. 2011;18(1):192-8.
48. Martin RC, Howard J, Tomalty D, Robbins K, Padr R, Bosnjakovic PM, et al. Toxicity of irinotecan-eluting beads in the treatment of hepatic malignancies: results of a multi-institutional registry. Cardiovasc Intervent Radiol. 2010;33(5):960-6.
49. Martin RC, 2nd, Scoggins CR, Tomalty D, Schreeder M, Metzger T, Tatum C, et al. Irinotecan drug-eluting beads in the treatment of chemo-naive unresectable colorectal liver metastasis with concomitant systemic fluorouracil and oxaliplatin: results of pharmacokinetics and phase I trial. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2012;16(8):1531-8.
50. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205- 16.
51. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.