SCRI DEVELOPMENT INNOVATIONS

GI 189

A Two Arm Safety Study of Regorafenib before or after SIR-Spheres® Microspheres (^{90}Y) for the Treatment of Patients with Refractory Metastatic Colorectal Cancer and Liver Metastases

SCRI INNOVATIONS STUDY NUMBER:	GI 189
STUDY DEVICE:	SIR-Spheres®[1] Microspheres
SPONSOR:	SCRI Development Innovations, LLC (SCRI Innovations) 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@scresearch.net
STUDY CHAIR:	Andrew Kennedy, MD Sarah Cannon Research Institute (SCRI) 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI
STUDY CO-CHAIR:	Johanna Bendell, MD Sarah Cannon Research Institute (SCRI) 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI
MEDICAL MONITOR	D.K. Strickland, MD SCRI Innovations 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-901-309-2572 asksarah@scresearch.net
DATE FINAL:	16 December 2013
AMENDMENT 1 DATE:	15 April 2014

[1] SIR-Spheres is a registered trademark of Sirtex SIR-Spheres Pty Ltd

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Clinical Study Statement of Compliance

A Two Arm Safety Study of Regorafenib before or after SIR-Spheres® Microspheres (^{90}Y) for the Treatment of Patients with Refractory Metastatic Colorectal Cancer and Liver Metastases

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 812, Investigational Device Exemptions**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

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Clinical Study Principal Investigator Signature Page

A Two Arm Safety Study of Regorafenib before or after SIR-Spheres® Microspheres (^{90}Y) for the Treatment of Patients with Refractory Metastatic Colorectal Cancer and Liver Metastases

SCRI INNOVATIONS STUDY NUMBER:		GI 189	
STUDY DRUG(S):		SIR-Spheres® Microspheres	
DATE FINAL:		16 December 2013	
AMENDMENT NUMBER:	**1**	**AMENDMENT DATE:**	15 April 2014

Principal Investigator Name Please Print	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

SCRI Development Innovations, LLC
3322 West End Avenue, Suite 900
Attn: GI 189 Study Team
Nashville, TN 37203

SCRI Innovations GI 189 Clinical Study Summary of Changes

AMENDMENT NUMBER:	1	**AMENDMENT DATE:**	15 April 2014

Global Changes

In-text references to appendices have been reordered to adjust for the change of Appendix E to A and Appendix F to B.

Informed consent forms for both cohorts have been adjusted to reflect updates to the protocol.

Section 3.1 Inclusion Criteria and Synopsis

10. Male patients with female partners of childbearing potential and ~~women~~ female patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 30 days following last dose. Male patients must also refrain from donating sperm during their participation in the study.

Section 5 Study Design, Section 5.4 Correlative Testing and Synopsis

Blood samples will be collected from all patients **prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, on Day 8 after SIR-Spheres treatment, and Day 30 (pre-dose) after SIR-Spheres treatment (see Section 5.1).** ~~prior to SIR-Spheres administration on Day 1, Day 8, and Day 30 (pre-dose) following SIR-Spheres treatment.~~

Cytokine analyses will include, **but not be limited to**, the following:

Section 5 Study Design Figure 1 GI 189 Schema

Cohort 1 Regorafenib then SIR-Spheres (n=25)

CYCLE	**1**			~~**2**~~	**2**		**3***	~~**3**~~			**4**	~~**4**~~
WEEK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	~~**12**~~
Regorafenib 160 mg PO daily	X	X	X	-	-	-	X	X	X	~~X~~	X	-
SIR-Spheres	-	-	-		X	-	-	-	-	-	-	-

Regorafenib - 160 mg orally once daily for Days 1-21 of a 28-day cycle followed by a 1 week washout, then treatment with SIR-Spheres microspheres followed by a 2-week rest*, followed by re-initiation of regorafenib. *If liver function toxicities are present, patient may be rechecked weekly for 2 additional weeks **to allow for appropriate resolution of liver function toxicities prior to re-starting regorafenib.**

Cohort 2 SIR-Spheres then Regorafenib (n=25)

CYCLE	1		2*		~~2~~		3	~~3~~			4	4
WEEK	1	2	3	4	5	6	7	8	9	10	11	12
SIR-Spheres	X	-	-	-	-	-	-	-	-	-	-	-
Regorafenib 160 mg PO daily	-	-	X	X	X	-	X	X	X	~~X~~	X	-

Treatment with SIR-Spheres microspheres followed by a 2-week rest*
then regorafenib initiated - 160 mg orally once daily for Days 1- 21 of each 28-day cycle. * If liver function toxicities ~~(LFTs)~~ are present, patient may be rechecked weekly for 2 additional weeks and ~~re~~initiation of regorafenib may be delayed until appropriate resolution of **liver function toxicities** ~~LFTs~~.

Section 7 Study Assessments and Evaluations

Overview

The Screening physical examination, medical history, ECOG PS, complete blood counts (CBC), differential and platelets, comprehensive metabolic profile (CMP), and prothrombin time/partial thromboplastin time/international normalized ratio (PT/PTT/INR) should be done ≤21 days prior to initiation of treatment. ~~However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated on Cycle 1 Day 1.~~

~~Section 7.2 Baseline Assessments~~

This section has been listed separately for the two cohorts as Section 7.3.1 for Cohort 1 and Section 7.4.1 for Cohort 2.

Section 7.2 Patient Assessment for SIR-Spheres

- Cohort 1 patients will have these assessments performed during week **4** ~~5~~ prior to SIR-spheres treatment.
- Cohort 2 patients will be assessed at Screening **7-4 days prior to SIR-Spheres treatment on CID1.**

Section 7.3.1 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at Screening ≤21 days prior to initiation of treatment unless otherwise noted:

- **Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)**

Section 7.3.1 Baseline Study Assessments (continued)

- **Medical history**
- **Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, respiratory rate, and oral temperature)**
- **Blood pressure (BP)**
- **ECOG PS (Appendix D)**
- **Concomitant medication review**
- **CBC (complete blood count) including hemoglobin, hematocrit, white blood cell (WBC) with 3-part differential, and platelets**
- **CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin plus lactate dehydrogenase (LDH), and phosphorous.**
- **PT/PTT/INR**
- **Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)**
- **Disease assessments:**
  - **CT scan chest, abdomen, and pelvis (≤28 days prior to treatment)**
  - **CEA tumor marker**

Section 7.3.2 Cycle 1, Day 1

- ~~AE assessment~~

Section 7.3.4 Cycle 1, Day 22 (assessments to be completed ≤7 days prior to SIR-Spheres treatment)

- **Physical examination, weight, and vital signs**
- BP
- **ECOG PS**
- **AE assessment**
- **Concomitant medication review**
- **CBC**

Section 7.3.4 Cycle 1, Day 22 (assessments to be completed ≤7 days prior to SIR-Spheres treatment) (continued)

- **CMP**
- **PT/PTT/INR (for patients receiving Coumadin therapy)**
- Biomarker blood sample collection **prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan**
- CEA tumor marker

The following tests will be obtained 7-4 days prior to SIR-Spheres treatment:

- **Hepatic angiogram**
- **^{99m}Tc MAA lung shunt scan**

Section 7.3.5 Cycle 2, Day 1 ~~(±72 hours) (Day of SIR-Spheres treatment)~~

- **SIR-Spheres treatment**
- BP
- ~~Physical examination, weight, and vital signs~~
- ~~BP~~
- ~~ECOG PS~~
- ~~AE assessment~~
- ~~Concomitant medication review~~
- ~~CBC~~
- ~~CMP~~
- ~~PT/PTT/INR (for patients receiving Coumadin therapy)~~
- ~~Biomarker blood sample collection~~
- ~~CEA tumor marker~~

Section 7.3.6 Cycle 2, Day 8

- Biomarker blood sample collection **(following SIR-Spheres treatment)**

~~Section 7.4.6 Cycle 2, Day 15~~
and Schedule of Assessments – Cohort 1 table

- ~~CMP~~
- ~~PT/PTT/INR (for patients receiving Coumadin therapy)~~

~~**Section 7.4.7 Cycle 2, Day 22 (if LFT toxicity persists)**~~

- ~~CMP~~

Section 7.3.7 Cycle 3 and Beyond, Day 1 (±72 hours)

Regorafenib may not start until the patient's hematologic, liver and renal functions have been re-confirmed as eligible according to the Section 3.1 by the Investigator. **Therefore, the regorafenib cycle starts on the day that treatment begins. If liver function toxicities are present, patient may be rechecked weekly for 2 additional weeks. Those patients with persistent liver function toxicities after this time will come off study, but will be followed until resolution.**

- Biomarker blood sample collection (Day 30 **[pre-dose]** ~~**only**~~ **following SIR-Spheres treatment)**

Section 7.4 Study Treatment Assessments – COHORT 2

~~SIR-Spheres followed by 2-4 week rest then regorafenib~~

Section 7.4.1 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at Screening ≤21 days prior to initiation of treatment unless otherwise noted. ~~If t~~The following ~~**are**~~**must be repeated or** performed ~~≤within~~ 7 days of Cycle 1 Day 1 ~~they do not have to be repeated~~ **to document Cycle 1 Day 1 assessments prior to SIR-Spheres treatment unless otherwise noted**:

- **Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)**
- **Medical history**
- **Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, respiratory rate, and oral temperature)**
- **Blood pressure (BP)**
- **ECOG PS (Appendix D)**
- **Concomitant medication review**
- **CBC (complete blood count) including hemoglobin, hematocrit, white blood cell (WBC) with 3-part differential, and platelets**

- **CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT,**

Section 7.4.1 Baseline Study Assessments (continued)

- **total bilirubin, total protein, and albumin plus lactate dehydrogenase (LDH), and phosphorus.**
- **PT/PTT/INR**
- **Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)**
- **Biomarker blood sample collection prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, which will be obtained 7-4 days prior to SIR-Spheres treatment**
- **Disease assessments:**
  - **CT scan chest, abdomen, and pelvis (≤ 28 days prior to treatment)**
  - **CEA tumor marker**

Section 7.4.2 Cycle 1, Day 1 ~~(Day of SIR-Spheres treatment)~~

- **SIR-Spheres treatment**
- ~~AE assessment~~
- ~~Biomarker blood sample collection~~
- ~~Medical History~~
- ~~Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, respiratory rate, and oral temperature)~~
- ~~BP~~
- ~~ECOG PS~~
- ~~Concomitant medication review~~
- ~~CBC~~
- ~~CMP~~
- ~~PT/PTT/INR (for patients receiving Coumadin therapy)~~
- ~~Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)~~
- ~~CEA tumor marker~~

Section 7.4.3 Cycle 1, Day 8

- Biomarker blood sample collection **(following SIR-Spheres treatment)**
- ~~**Section 7.5.3 Cycle 1, Day 15**~~
- ~~CMP~~
- ~~PT/PTT/INR (for patients receiving Coumadin therapy)~~

~~**Section 7.5.4 Cycle 1, Day 22 (if LFT toxicity persists)**~~

- ~~CMP~~

Section 7.4.4 Cycle 2, Day 1 (±72 hours)

Regorafenib may not start until the patient's hematologic, liver and renal functions have been re-confirmed as eligible according to Section 3.1 by the Investigator. Therefore, the regorafenib cycle starts on the day that treatment begins. **If liver function toxicities are present, patient may be rechecked weekly for 2 additional weeks. Those patients with persistent liver function toxicities after this time will come off study, but will be followed until resolution.**

Section 8.1.3 Precautions and Risks Associated with SIR-Spheres® Microspheres

There is some evidence that there is a decrease in leucocyte levels, with a nadir **eight** ~~8~~ weeks after implantation. This has been evident in both first line and refractory studies. ~~with studies reporting a~~ **The** median number of leukocytes **was** ~~of~~ 3.55 x 10^9/L ~~(3.55 x 10^3/µL)~~ (NCIC CTC3 ~~g~~**G**rade 1). Leukocyte levels recover from this point, with the median value rising to normal levels 4-8 weeks after the decline.

~~Please refer to PMA P990065 SIR-Spheres® microspheres for a comprehensive review of prior clinical, laboratory and animal investigations concerning the device.~~

Section 8.2 Regorafenib

Regorafenib is to be administered in accordance with the ~~terms of its marketing authorization~~ **recommendations in the approved labelling** and in accordance with institutional standard of practice.

Section 10.1 Statistical Design

The safety of two treatment cohorts will be evaluated in the open-label study. The administration sequence of radioembolization with SIR-Spheres ~~to the patient with~~ **and** regorafenib is different in the two treatment cohorts.

Appendix ~~E~~ A: Schedule of Assessments – Cohort 1 – Regorafenib then SIR-Spheres then Regorafenib

Cycle 1 Day 22 and Cycle 2 Day 1

Following assessments added to C1D22 and removed from C2D1: physical exam, ECOG performance status, adverse event evaluation, concomitant medication review, CBC, CMP, PT/PTT/INR, biomarker blood sample collection, tumor marker, hepatic angiogram, and ^{99m}Tc MAA lung shunt scan.

Appendix A ~~E~~: Schedule of Assessments tables

Footnotes:

[h] Biomarker samples (see Section 5.4) will be collected ~~prior to SIR-Spheres administration on Day 1, Day 8, and Day 30 (pre-dose) following SIR-Spheres treatment.~~ from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, which will be obtained 7-4 days prior to

Appendix A ~~E~~: Schedule of Assessments tables

SIR-Spheres treatment [see Section 7.2]), on Day 8 after SIR-Spheres radiation, and Day 30 (pre-dose) after SIR-Spheres radiation.

[f] If ~~LFTs~~ **liver function toxicities** are present after a 2 week rest, then patients ~~may~~ **must** be rechecked weekly for 2 additional weeks.

[o] ~~Cohort 1~~ ~~p~~Patients will be assessed 7-**4 days prior to SIR-Spheres treatment** to determine the suitability for SIR-Spheres (see Section 7.2).

[q] **The Cycle 1 Day 22 physical examination, ECOG performance status, CBC, CMP, and PT/PTT/INR, tumor marker (CEA), adverse event evaluation, and concomitant medication review to be completed ≤7 days prior to SIR-Spheres radiation treatment.**

Appendix ~~F~~ B: Schedule of Assessments – Cohort 2-SIR-Spheres then Regorafenib

Baseline assessment of **biomarker blood sample collection** added.

Cycle 1 Day 1 assessments removed.

Footnotes

[b] The Screening physical examination, update of medical history, ECOG performance status, CBC, CMP, and PT/PTT/INR, ~~serum or urine pregnancy test~~ and concomitant medication review **and tumor marker (CEA)** should be done ≤21 days prior to initiation of treatment. ~~However, if These initial examinations are obtained within 72 hours of Cycle Day 1 they do not have to be repeated on Cycle 1 Day 1.~~ **These initial examinations must be repeated or performed ≤7 days of Cycle 1 Day 1 to document Cycle 1 Day 1 assessments prior to SIR-Spheres treatment.** CT scans to document measurable or evaluable disease (i.e. tumor measurement) and tumor marker (CEA) should be performed ≤28 days prior to initiation of treatment. ~~Cohort 2~~

Appendix ~~F~~ B: Schedule of Assessments – Cohort 2-SIR-Spheres then Regorafenib
(continued)

~~p~~Patients will be assessed at Screening **(4-7 days prior to SIR-Spheres treatment)** to determine the suitability for SIR-Spheres (see Section 7.2).

[f] If ~~LFTs~~ **liver function toxicities** are present after a 2 week rest, then patients ~~may~~ **must** be rechecked weekly for 2 additional weeks **prior to Regorafenib treatment on C2D1**.

[h] Biomarker samples (see Section 5.4) will be collected ~~prior to SIR-Spheres administration on Day 1, Day 8, and Day 30 (pre-dose) following SIR-Spheres treatment.~~ from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, which will be obtained 7-4 days prior to SIR-Spheres treatment [see Section 7.2]), on Day 8 after SIR-Spheres radiation, and Day 30 (pre-dose) after SIR-Spheres radiation.

[p] Blood pressure is required Cycle 3 Day 8. Cycle 4 and beyond, blood pressure will be required Day 1 only.

GI 189 PROTOCOL SYNOPSIS

Title of Study:	A Two Arm Safety Study of Regorafenib before or after SIR-Spheres® Microspheres (^{90}Y) for the Treatment of Patients with Refractory Metastatic Colorectal Cancer and Liver Metastases
SCRI Innovations Study Number:	GI 189
Sponsor:	SCRI Development Innovations, LLC
Study Duration:	The total duration of the study is planned to be 16 months. **Phase of Study:** II
Study Centers:	This study will be conducted at approximately 5 sites in the United States in the SCRI network.
Number of Patients:	Up to 50 patients are planned to be enrolled in this study.
Objectives:	**Primary Objective** The primary objective of this study is: • To evaluate the safety of two treatment cohorts combining regorafenib and SIR-Spheres microspheres (SIR-Spheres) radioemoblization in patients with refractory metastatic colorectal cancer (mCRC) with liver metastasis. **Secondary Objectives** The secondary objective of this study is: • To evaluate the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) of patients with refractory mCRC when treated with combination SIR-Spheres and regorafenib in the two sequencing cohorts **Exploratory Objectives** The exploratory objective of this study is: • To evaluate the status of exploratory biomarkers and correlate with clinical outcomes of patients treated in one of two SIR-Spheres and regorafenib cohorts.
Study Design:	This is an open-label study comparing the safety of two treatment cohorts in which radioembolization will be administered using the device SIR-Spheres microspheres (^{90}Y resin microspheres) in combination with regorafenib to patients with mCRC with liver metastases. The two treatment cohorts will be evaluated for safety, ORR, PFS, and OS. Twenty-five patients will be treated in each cohort. The first cohort will complete enrollment before the second cohort opens. There will be no randomization or blinding. Blood samples will be collected from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, on Day 8 after SIR-Spheres treatment, and Day 30 (pre-dose) after SIR-Spheres treatment (see Section 5.1). Expressions of cytokines and proteins will be measured to explore potential biomarkers that may correlate with clinical outcome.
Study Drugs, Doses, and Modes of Administration:	Two treatment cohorts will be evaluated sequentially as follows: **Cohort 1** Regorafenib (one cycle) followed by SIR-Spheres followed by re-initiation of regorafenib 2-4 weeks after SIR-Spheres **Cohort 2** SIR-Spheres followed by regorafenib to start 2-4 weeks after SIR-Spheres All patients will take regorafenib, orally once-a-day, on Days 1-21 of a 28-day treatment cycle. Twenty-five patients will be treated in each cohort.

GI 189 PROTOCOL SYNOPSIS

Inclusion Criteria:	1. Histologically confirmed metastatic adenocarcinoma of the colon or rectum. 2. Patients who have been previously treated with or are not candidates for fluorouracil, oxaliplatin, irinotecan, and if Kras wild-type, anti EGFR therapy 3. Considered an appropriate candidate for regorafenib therapy. 4. Measurable disease or evaluable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix C). 5. Measurable computed tomography (CT) scan evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent at the time of study entry. 6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-1 (Appendix D). 7. Adequate hematologic function defined as: – Absolute neutrophil count (ANC) ≥1500/μL – Hemoglobin (Hgb) ≥9 g/dL (pre-enrollment transfusion allowed) – Platelets ≥75,000/μL 8. Adequate liver function defined as: – Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) or <5 x ULN if due to hepatic metastases – Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin) 9. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated creatinine clearance ≥50 mL/min. 10. Male patients with female partners of childbearing potential and female patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 30 days following last dose. Male patients must also refrain from donating sperm during their participation in the study (Appendix E). 11. Life expectancy ≥ 3 months. 12. Age ≥18 years. 13. Ability to understand the nature of this study and give written informed consent.

Exclusion Criteria:	1. Most recent chemotherapy ≤14 days and ≥Grade 1 chemotherapy-related side effects, with the exception of alopecia. 2. Use of a study drug ≤21 days or 5 half-lives (whichever is shorter) prior to initiation of study treatment. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of study treatment is required. 3. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy. 4. Previous radiation delivered to the upper abdomen. 5. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement. 6. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks previously and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy. 7. Leptomeningeal metastases or spinal cord compression due to disease. 8. Pregnant or lactating. 9. Evidence of ascites, cirrhosis, portal hypertension, or thrombosis as determined by clinical or radiologic assessment. 10. History of abdominal fistula or gastrointestinal perforation ≤6 months prior to beginning study treatment. 11. Serious non-healing wound, active ulcer, or untreated bone fracture. 12. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome). 13. Any of the following cardiac diseases currently or within the last 6 months: – Unstable angina pectoris – Congestive heart failure (NYHA ≥ Grade 2 [Appendix F]) – Conduction abnormality not controlled with pacemaker or medication – Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible) – Valvular disease with significant compromise in cardiac function

Exclusion Criteria: (continued)	14. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment). 15. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. 16. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C. 17. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 18. Use of strong CYP34A inducers or inhibitors (see Appendix G). 19. The herbal medications St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng will not be allowed during study treatment. Patients should stop using these herbal medications 7 days prior to first dose of study drug. 20. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 21. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.
Correlative Testing:	Blood samples will be collected from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, on Day 8 after SIR-Spheres treatment, and Day 30 (pre-dose) after SIR-Spheres treatment (see Section 7.2). Expressions of cytokines and proteins will be measured to explore potential biomarkers that may correlate with clinical outcome. Cytokine analyses will include, but not be limited to, the following: VEGFA, VEGFC, VEGFD, FGF2, HGF, EGF, PDGF-AA, PDGF-AB/BB, MMP-9, sVEGFR-2, E-selectin, VCAM-1, ICAM-1, MIF, TNFα, IFN-α and -γ, LIF, TGF-α, TGF-β1, Angiopoietin-2, Endoglin, IGF, Osteopontin, GM-CSF, G-CSF, M-CSF, SCGF-β, SCF, Beta-NGF, PlGF, MCP-1, MCP-3, RANTES, MIP-1α, MIP-1β, MIG, Eotaxin, IP-10, SDF-1α, GRO-α, CTACK, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 p40, IL-12 p70, IL-16, CA9 and HIF-1 alpha. Protein expression in blood samples will be measured by proteomics platform.
Statistical Methodology:	There is no formal hypothesis testing in this study. The sample size of 50 patients (25 in each cohort) is based on clinical practicalities rather than statistical reasoning, in order to evaluate the safety of the 2 different sequences in treatment administration of SIR-Spheres microspheres and regorafenib. With 25 patients per cohort, the 95% confidence interval for the response rate estimate would be no more than 21%.

GI 189 CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST	Aspartate aminotransferase
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CMP	Comprehensive metabolic profile
CRC	Colorectal cancer
CRC	Complete remission
CT	Computerized tomography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LFT	Liver Function Test
mCRC	metastatic Colorectal Cancer
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response rate
OS	Overall Survival
PD	Progressive disease
PHI	Protected health information
PFS	Progression-free survival
PMA	Premarket approval
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SIRT	Selective internal radiation therapy
ULN	Upper limit of normal

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1. INTRODUCTION

The American Cancer Society estimates that 142,820 new cases of colorectal cancer (CRC) will be diagnosed in the United States in 2013. Although new treatments and frequent screenings have decreased mortality rates over the past 30 years, it is estimated that 50,830 patients will succumb to the disease in 2013. Colorectal cancer remains the third most frequently diagnosed cancer in the United States and is responsible for 9% of all cancer deaths (American Cancer Society 2013).

The population of patients with refractory metastatic colorectal cancer (mCRC) in the U.S. is around 25,000 patients. Once patients have exhausted available standard therapies, their average survival is 4-6 months, and many have a performance status of Eastern Cooperative Oncology Group (ECOG) 1. Findings from previous Phase III trials of panitumumab versus best supportive care (BSC) and cetuximab versus BSC, in patients with refractory mCRC suggested a median progression-free survival (PFS) of two months and overall survival (OS) of approximately 5 months (Van Cutsem et al. 2007, Jonker et al. 2007). Recently, regorafenib ([Stivarga] Bayer HealthCare Pharmaceuticals, Inc.) was approved for the treatment of patients with mCRC. This was based on an improvement in OS of 6.4 versus 5.0 months (HR 0.77). The PFS of patients on regorafenib was 1.9 months versus 1.7 months for placebo (Grothey et al. 2012). Antiangiogenic drugs like regorafenib have been thought to act primarily as tumor-static agents by preventing the growth of new tumor blood vessels. Other antiangiogenic agents such as bevacizumab have been and are being evaluated in the maintenance setting during first line therapy for mCRC.

1.1 Background

Recent targeted therapies and treatment strategies have shown promise in CRC but elimination of disease once spread to the liver remains a challenge. The main cause of death in over 50% of CRC patients is liver metastases (Silverberg 1977). Preoperative chemotherapy may improve resectability but may also impact overall survival. Postoperative complications have been associated with decreased long-term survival after surgery for CRC with liver metastases with curative intent (Mavros et al. 2013).

Radioembolization also referred to as selective internal radiation therapy (SIRT) enables multiple hepatic metastases to be targeted in a single procedure (Hendlisz et al. 2010). Through fluoroscopic guidance, radioembolization can be achieved with the insertion of an intra-vascular catheter in the groin threaded through the arteries until it reaches the hepatic artery. Yttrium- 90 (^{90}Y) microspheres are released through the catheter to lodge in the small vessels that feed the tumor, stopping blood flow and emitting radiation. Radioembolization aims to deliver target radiation to all tumors in the liver while limiting the dose to the liver parenchyma (Kennedy et al. 2012).

SIR-Spheres® microspheres (^{90}Y-resin microspheres) are approved by the Food and Drug Administration (FDA), and a number of safety and efficacy studies have been conducted in patients with mCRC with liver metastases.

A randomized study of 46 mCRC patients with liver metastases revealed that a single hepatic arterial injection of ^{90}Y-resin microspheres combined with intravenous (IV) infusion 5-fluorouracil (5-FU) improved time to overall disease progression. Forty-four eligible patients were randomized to Arm A (n = 23) IV infusion 5-FU 300 mg/m^2 on days 1-14 every 3 weeks; or Arm B (n = 21) radioembolization plus IV infusion 5-FU 225 mg/m^2 on days 1 through 14 then 300 mg/m^2 days 1-14 every 3 weeks. Treatment continued until hepatic progression and cross-over to radioembolization was permitted for patients in Arm A. Ten patients in Arm A crossed-over at progression. Median OS was 7.3 and 10.0 months in arms A and B, respectively (Hendlisz et al. 2010).

1.2 Rationale for the Study

Radioembolization using SIR-Spheres microspheres (SIR-Spheres) to treat liver-only or liver-dominant mCRC has been successful in this refractory setting. The combination of regorafenib and SIR-Spheres is an attractive option as an anti-tumor and maintenance treatment for the refractory CRC population.

The proper sequencing of this combination of regorafenib and SIR-Spheres is currently unclear. We propose this two arm study (25 patients in each arm) to evaluate the safety of the combination of regorafenib and SIR-Spheres, with one cohort of patients receiving regorafenib for three weeks followed by a one week hold of regorafenib (regorafenib half-life is 28 hours, one week to allow for washout), followed by SIR-Spheres treatment, followed by re-initiation of regorafenib two to four weeks later, and the other cohort of patients receiving SIR-Spheres followed by the initiation of regorafenib two to four weeks later.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is:

- To evaluate the safety of two treatment cohorts combining regorafenib and SIR-Spheres in patients with refractory mCRC with liver metastasis.

2.2 Secondary Objective

The secondary objective of this study is:

- To evaluate the overall response rate (ORR), progression-free survival (PFS), and OS of patients with refractory mCRC when treated with combination SIR-Spheres and regorafenib in the two sequencing cohorts.

2.3 Exploratory Objectives

The exploratory objective of this study is:

- To evaluate the status of exploratory biomarkers and correlate with clinical outcomes of patients treated in the two SIR-Spheres and regorafenib cohorts.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Histologically confirmed metastatic adenocarcinoma of the colon or rectum.
2. Patients who have been previously treated with or are not candidates for fluorouracil, oxaliplatin, irinotecan, and if Kras wild-type, anti EGFR therapy
3. Considered an appropriate candidate for regorafenib therapy.
4. Measurable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix C)**.**
5. Measurable computed tomography (CT) scan evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent at the time of study entry.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0-1 (Appendix D).
7. Adequate hematologic function defined as:
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Hemoglobin (Hgb) ≥9 g/dL (pre-enrollment transfusion allowed)
   - Platelets ≥75,000/μL
8. Adequate liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) or <5 x ULN if due to hepatic metastases
   - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
9. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated creatinine clearance ≥50 mL/min.
10. Male patients with female partners of childbearing potential and female patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 30 days following last dose. Male patients must also refrain from donating sperm during their participation in the study (Appendix E).
11. Life expectancy ≥ 3 months.
12. Age ≥18 years.
13. Ability to understand the nature of this study and give written informed consent.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Most recent chemotherapy ≤14 days and ≥Grade 1 chemotherapy-related side effects, with the exception of alopecia.
2. Use of a study drug ≤21 days or 5 half-lives (whichever is shorter) prior to initiation of study treatment. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of study treatment is required.
3. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.
4. Previous radiation delivered to the upper abdomen.
5. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.
6. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks previously and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy.
7. Leptomeningeal metastases or spinal cord compression due to disease.
8. Pregnant or lactating.
9. Evidence of ascites, cirrhosis, portal hypertension, or thrombosis as determined by clinical or radiologic assessment.
10. History of abdominal fistula or gastrointestinal perforation ≤6 months prior to beginning study treatment.
11. Serious non-healing wound, active ulcer, or untreated bone fracture.
12. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome).
13. Any of the following cardiac diseases currently or within the last 6 months:
    - Unstable angina pectoris
    - Congestive heart failure (NYHA ≥ Grade 2 [Appendix F])
    - Conduction abnormality not controlled with pacemaker or medication
    - Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

- Valvular disease with significant compromise in cardiac function

14. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment).
15. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
16. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C.
17. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
18. Use of strong inducers or inhibitors of CYP34A (see Appendix G).
19. The herbal medications St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng will not be allowed during study treatment. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
20. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
21. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)
- Inability of the patient to comply with study requirements or lost-to-follow-up
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Pregnancy

After discontinuation from protocol treatment, patients must be followed for adverse events (AEs) for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these

values are not likely to improve, because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0 insert current version number) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the eCRF.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee (Institutional Review Board/Ethics Committee) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study and sign consent will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the SCRI Development Innovations (SCRI Innovations) Central Enrollment Desk. The enrollment desk may be reached at the following: CANN.SCRIInnovationsEnr@scri-innovations.com OR FAX to: 1-866-346-1062 or 615-524-4012. Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed via email within 24 hours, or by the next business day.

5. STUDY DESIGN

This is an open-label study comparing the safety of two treatment cohorts in which radioembolization will be administered using the device SIR-Spheres in combination with regorafenib to patients with mCRC with liver metastases. The two treatment cohorts will be evaluated for safety, ORR, PFS, and OS. Twenty-five patients will be treated in each cohort. The first cohort will complete enrollment before the second cohort opens. There will be no randomization or blinding.

A safety review for toxicity by the Medical Monitor will occur after the first 10 patients have been enrolled in each cohort and treated with one cycle of regorafenib and SIR-spheres (combination therapy) to assess the frequency of ≥ Grade 3 adverse events and all SAEs. Accrual will not be halted while the analysis is being conducted.

Stopping Rules Due to Toxicities of Combination Therapy

Stopping rules due to toxicities assessed as related to combination therapy by the Medical Monitor will be defined as follows:

- A patient death considered to be caused by AEs of combination therapy
- A patient with Grade 4 AST, ALT, or irreversible hepatic failure assessed as related to combination therapy;
- More than 2 patients that develop Grade 3 AST, ALT, or total bilirubin assessed as related to combination therapy;
- More than 2 patients develop Grade 3 bleeding in the lung, stomach, small intestine, or liver assessed as related to combination therapy.

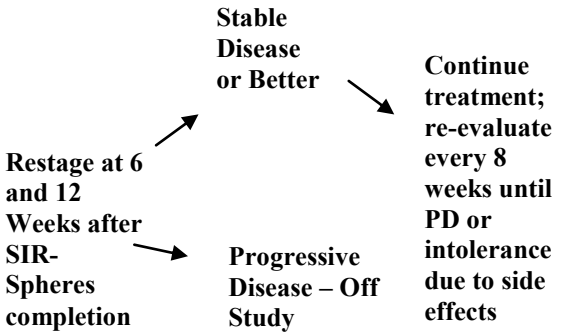
If the early stopping rules are met or safety signals emerge from the group of the first 10 patients treated with combination therapy in each cohort, patient recruitment will discontinue and the study will be reassessed. Any outcome of these safety reviews will be communicated in a timely manner to the participating investigators so that they may notify their IRBs.

Blood samples will be collected from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, on Day 8 after SIR-Spheres treatment, and Day 30 (pre-dose) after SIR-Spheres treatment (see Section 5.1). Expressions of cytokines and proteins will be measured to explore potential biomarkers that may correlate with clinical outcome. The study schema is presented in Figure 1.

Figure 1 GI 189 Schema

Cohort 1 Regorafenib then SIR-Spheres (n=25)

CYCLE	1				2		3*				4
WEEK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Regorafenib 160 mg PO daily	X	X	X	-	-	-	X	X	X	-	X
SIR-Spheres	-	-	-	-	X	-	-	-	-	-	-

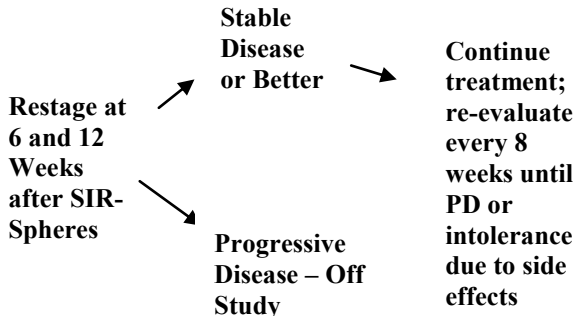


Regorafenib - 160 mg orally once daily for Days 1-21 of a 28-day cycle followed by a 1 week washout, then treatment with SIR-Spheres microspheres followed by a 2 week rest*, followed by re-initiation of regorafenib.
***If liver function toxicities are present, patient may be rechecked weekly for 2 additional weeks to allow for appropriate resolution of liver function toxicities prior to re-starting regorafenib.**

NOTE: COHORT 1 ENROLLMENT WILL BE COMPLETED BEFORE COHORT 2 OPENS TO ENROLLMENT

Cohort 2 SIR-Spheres then Regorafenib (n=25)

CYCLE	1		2*				3				4
WEEK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
SIR-Spheres	X	-	-	-	-	-	-	-	-	-	-
Regorafenib 160 mg PO daily	-	-	X	X	X	-	X	X	X	-	X



Treatment with SIR-Spheres microspheres followed by a 2 week rest* then regorafenib initiated - 160 mg orally once daily for Days 1- 21 of each 28-day cycle.
***If liver function toxicities are present, patient may be rechecked weekly for 2 additional weeks and initiation of regorafenib may be delayed until appropriate resolution of liver function toxicities.**

5.1 Treatment Plan

Radioembolization using SIR-Spheres Microspheres

Patients must be assessed with a hepatic angiogram and "break-through" scan to determine suitability for SIR-Spheres.

Hepatic Angiogram

The patient will undergo a preliminary angiogram of the liver to determine the vascular anatomy of the liver. The hepatic angiogram will provide a road map of the arterial supply of the liver in order to plan delivery of the SIR-Spheres microspheres. The hepatic angiogram should be performed together with the 'break-through' scan and results must be available prior to radioembolization with SIR-Spheres (see Appendix Appendix A/Appendix B).

Liver-Lung Break-Through Nuclear Scan

In order to mitigate the possibility of including patients who exhibit excessive liver-to-lung shunting a nuclear medicine 'break-through' scan using ^{99m}Technetium (Tc) macroaggregated albumin will be performed in all patients prior to SIR-Spheres treatment. Excessive liver-to-lung shunting resulting in radiation damage to the lungs has not been observed in any case of colorectal metastatic liver disease treated since the premarket approval (PMA) of SIR-Spheres microspheres for mCRC in 2003.

If either the hepatic angiogram or the liver-lung break through nuclear scan shows that a patient is ineligible to receive SIR-Spheres, then the patient will be removed from study and replaced.

SIR-Spheres Microspheres Administration

SIR-Spheres microspheres will be administered by a certified radiation oncologist, interventional radiologist, or nuclear medicine physician to the patient by injection through a trans-femoral catheter into the hepatic artery. All areas of tumor within the liver will be targeted with SIR-Spheres microspheres which usually involves treating both lobes of the liver. However, it is vital that the SIR-Spheres microspheres are not delivered to other organs such as the duodenum, stomach, pancreas etc.

If the metastases are limited to only one lobe, the radiologist can insert the catheter selectively into the lobar artery supplying only that lobe that contains the metastases. The SIR-Spheres microspheres will then be delivered only to the lobe containing the metastases with sparing of the other normal lobe. The SIR-Spheres microspheres are injected slowly into the hepatic artery to avoid reflux back down the hepatic artery and placement in the pancreas, stomach and other organs.

After SIR-Spheres microspheres have been administered, the patient will be monitored closely during the following 2 week rest period prior to starting regorafenib (see Section 7). If liver function toxicities are present, the patient may be rechecked weekly for 2 additional weeks.

Regorafenib Administration

All patients entering this study will receive regorafenib at a dose of 160 mg orally once daily on Days 1-21 of each 28 day cycle.

Patients will be instructed to take regorafenib with a low-fat breakfast that contains less than 30% fat. Examples of a low-fat breakfast include 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly, and 8 ounces of skin milk (319 calories and 8.2 grams fat); or 1 cup of cereal, 8 ounces of skim milk, 1 slice of toast with jam, apple juice, and 1 cup of coffee or tea (520 calories and 2 grams fat). The time of day for administration of regorafenib should be consistent.

If the patient misses a dose of study drug, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due for once daily dosing. If the next dose is due in less than 12 hours for once daily the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking the study medication, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of regorafenib. If vomiting persists the patient should contact the investigator.

No routine prophylactic anti-emetics will be given. However, antiemetics may be administered with nausea and vomiting when they occur, and may be given prophylactically afterwards.

5.2 Treatment Duration

Patients will be evaluated for toxicity at the start of each 28-day cycle of regorafenib. Patients will be restaged at 6 weeks and 12 weeks after SIR-Spheres in both cohorts, and every 8 weeks thereafter, with imaging, laboratory chemistries, and tumor markers as defined in Appendix A and Appendix B**Error! Reference source not found.**. Patients will continue on treatment until progression as defined in Appendix C or intolerance to side effects.

5.3 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with anti-emetics is allowed according to standard practice guidelines. At each visit, the patient will be asked about any new medications he is taking or has taken after the start of the study drug.

All concomitant medications and significant non-drug therapies taken ≤14 days prior to the start of study drug should be recorded.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Use of bisphosphonates and receptor activator of nuclear factor kappa-B ligand

(RANKL) inhibitors like denosumab. Treatment with these agents must begin 1 day prior to study treatment or after treatment is initiated. Treatment with these agents cannot be initiated on Cycle 1 Day 1.

- Full dose Coumadin is allowed if required for the treatment of thromboembolic disease occurring after the patients have initiated study treatment. INR must be followed and managed on Day 1 and 15 of each treatment cycle.
- Low molecular weight heparin is allowed.
- Erythropoietic and granulocyte colony-stimulating factor (G-CSF) agents according to standard guidelines. Neutropenia/fever should be managed according to accepted guidelines.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Avoid concomitant use of strong CYP34A inducers (e.g., rifampin, phenytoin, carbamazepin, phenobarbital, and St John's wort). For the most updated information, visit the following website: http://medicine.iupui.edu/clinpharm/ddis/. (see Appendix G)
- Avoid concomitant use of strong CYP34A inhibitors (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole). For the most updated information, visit the following website: http://medicine.iupui.edu/clinpharm/ddis/. (see Appendix G)
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of regorafenib.

5.4 Correlative Studies

Blood samples for biomarker testing will be collected from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, which will be obtained 7-4 days prior to SIR-Spheres treatment (see Section 7.2), on Day 8 after SIR-Spheres treatment, and Day 30 (pre-dose) after SIR-Spheres treatment. Expressions of cytokines and proteins will be measured to explore potential biomarkers that may correlate with clinical outcome.

Cytokine analyses will include, but not be limited to, the following: VEGFA, VEGFC, VEGFD, FGF2, HGF, EGF, PDGF-AA, PDGF-AB/BB, MMP-9, sVEGFR-2, E-selectin, VCAM-1, ICAM-1, MIF, TNFα, IFN-α and -γ, LIF, TGF-α, TGF-β1, Angiopoietin-2, Endoglin, IGF, Osteopontin, GM-CSF, G-CSF, M-CSF, SCGF-β, SCF, Beta-NGF, PlGF, MCP-1, MCP-3,

RANTES, MIP-1α, MIP-1β, MIG, Eotaxin, IP-10, SDF-1α, GRO-α, CTACK, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 p40, IL-12 p70, IL-16, CA9 and HIF-1 alpha.

Protein expression in blood samples will be measured by proteomics platform.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v4.0, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

6.1 Dose Modifications Due to Hematologic Toxicity

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Patients whose treatment is delayed due to toxicity will discontinue study drug or will proceed with the next cycle of treatment when toxicity has improved (as long as the toxicity resolves within 3 weeks) according to the dose modifications below. Two dose reductions for toxicity will be allowed. In addition, dose reductions will also be allowed based on clinical judgment of the treatment physician. If persistent toxicity occurs despite two dose reductions, the patient will be removed from the study.

Patients who require a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

Table 1 Regorafenib Dose Levels for Dose Modifications due to Toxicities

Dose Level	Regorafenib[a]
0	160 mg orally once daily
-1	120 mg orally once daily
-2	80 mg orally once daily

[a] Two dose reductions are allowed for regorafenib. Patients who require more than two dose reductions due to toxicity will be discontinued from the study.

The regorafenib dose modifications for hematologic toxicities are below in Table 2.

Table 2 Regorafenib Dose Modifications for Hematologic Toxicities

Toxicity	Regorafenib Dose[a]
Grade 3 And Recurrence of Grade 3	Hold dose until recovery to ≤ Grade 2, then resume regorafenib at one lower dose level.
Grade 4	Hold dose until recovery to ≤ Grade 2, then resume regorafenib at one lower dose level, or discontinue at the discretion of the investigator after discussion with the Medical Monitor.

[a] Any patient who requires a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient.

6.2 Regorafenib Dose Modifications for Non-Hematologic Toxicity

6.2.1 Regorafenib Dose Modifications for Abnormal Liver Function Tests

Regorafenib has been associated with severe drug-induced liver injury with fatal outcome in previous studies. Liver function tests (LFTs) will be monitored during study treatment as described in **Error! Reference source not found.** Appendix A and **Error! Reference source not found.**Appendix B. Dose modifications for regorafenib are recorded in Table 3 below.

Table 3 Regorafenib Dose Modifications for Abnormal Liver Function Tests

Toxicity	Regorafenib Dose
Baseline - Grade 1 And Recurrence OR Baseline Grade 1 – Grade 2 And Recurrence	Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.
Baseline - Grade 2	Hold dose until ≤ Grade 1 and check AST, ALT and bilirubin 2x/week. Resume regorafenib at 1 lower dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.[a]
Recurrence of Baseline - Grade 2	Discontinue regorafenib[b].
Baseline Any Grade-Grade 3	Hold dose until ≤ Grade 1 for baseline - Grade 1 OR until Grade 2 if baseline was Grade 2.

	Check AST, ALT and bilirubin 2x/week. Resume regorafenib at 1 lower dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.[a] Note: If ALT or AST >8 x ULN with a concomitant rise in bilirubin (of any degree) compared to previous bilirubin values, consider permanent discontinuation at the first occurrence[b.]
Recurrence of Baseline Any Grade-Grade 3	Discontinue regorafenib[b].
Baseline Any Grade-Grade 4	Discontinue regorafenib[b]

[a] If all values remain stable for 2 full cycles, dose re-escalation may be considered at the discretion of the investigator. After re-escalation AST, ALT, and bilirubin should be checked 2x/week for 2 weeks, followed by weekly assessments for at least 4 weeks.

[b] In case of discontinuation, AST, ALT, and bilirubin should be checked 2x/week for 2 weeks, followed by weekly assessments until recovery to baseline.

6.2.2 Regorafenib Dose Modifications for Hand-Foot Skin Reaction

Hand-foot skin reaction is a known adverse event for regorafenib. The dose modifications are provided in Table 4 below.

Table 4 Regorafenib Dose Modifications for Hand-Foot Skin Reaction

Toxicity	Regorafenib Dose
Grade 1 Numbness, dysesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Institute supportive measures immediately for symptomatic relief and continue treatment with the same dose level.
Grade 2 Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	First and Second Occurrence - Institute supportive measures immediately for symptomatic relief and decrease regorafenib one dose level (see Table 1) • If toxicity does not return to Grade 0-1 despite dose reduction, interrupt regorafenib for a minimum of 7 days until toxicity has resolved to Grade 0-1[a]. • If no improvement after 7 days, continue to hold until toxicity has resolved to Grade 0-1[a,b]. • When resuming treatment after a dose interruption, reduce regorafenib an additional dose level [a].

	Patients requiring >2 dose reductions will discontinue
Grade 3 Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	First and Second Occurrence - Institute supportive measures immediately for symptomatic relief and interrupt regorafenib for a minimum of 7 days and until toxicity resolved to Grade 0-1 (see Table 1). • When resuming treatment after dose interruption, decrease regorafenib by one dose level [a]. Patients requiring >2 dose reductions will discontinue protocol therapy.

[a]If toxicity returns to Grade 0-1 after dose level reduction, dose re-escalation is permitted at the discretion of the investigator
[b]If no recovery after 3 weeks of holding drug, patients should go off study unless in the opinion of the investigator & SCRI Innovations Medical Monitor, there is reason to believe that the patient is still experiencing clinical benefit.

The following supportive measurements should be considered for prevention and treatment of hand-foot skin reaction:

Control of callouses:

Before initiating treatment with regorafenib -

- Check condition of hands and feet
- Suggest a manicure/pedicure, when indicated
- Recommend pumice stone use for callous or rough spot removal

During regorafenib treatment -

- Avoid pressure points
- Avoid items that rub, pinch or create friction

Use of creams:

The following non-urea based creams should be applied liberally - Cetaphil, Aveeno, Udderly Smooth, Gold Bond, Norwegian Formula, and Eucerin.

The following keratolytic creams should be used sparingly and only to affected (hyperkeratotic) areas - urea-based creams and salicylic acid 6%.

Approximately 5-8% of A-hydroxy acids-based creams provide gentle chemical exfoliation. These creams should be applied liberally two times each day.

Topical analgesics like lidocaine 2% to be considered for pain control.

Topical corticosteroids like clobetasol 0.05% should be considered for subjects with Grade 2 or 3 hand-foot skin reaction. Avoid systemic steroids.

Cushions:

Protect tender areas by doing the following -

- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g., silicon, gel)

- Foot soaks with tepid water and Epsom salts

6.2.3 Regorafenib Dose Modifications for Hypertension

The dose modification table for treatment-emergent hypertension should be followed. Blood pressure measurements will be followed closely and appropriate treatment to effectively control hypertension is highly recommended.

Table 5 Regorafenib Dose Modifications for Hypertension

Toxicity	Antihypertensive Therapy	Regorafenib Dose
Grade 1 Prehypertension (systolic BP 120 – 139 mm Hg or diastolic BP 80 - 89 mm Hg)	None	No dose modification. Increase blood pressure monitoring.
Grade 2 Systolic BP 140 – 159 mm Hg or diastolic BP 90 -99 mm Hg, OR Symptomatic increase by >20 mm Hg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤90 mm Hg: If BP previously within normal limits, start antihypertensive monotherapy. If patient already on anti-hypertensive medication, titrate up the dose.	No dose modification. If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
Grade 3 Systolic BP ≥ 160 mm Hg or diastolic BP ≥100 mm Hg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤90 mm Hg: Start antihypertensive medication. AND/OR Increase current antihypertensive medication AND/OR Add additional antihypertensive medications.	Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve[a]. When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level[b]. If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level[c].
Grade 4 Life-threatening consequences (e.g. Malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Discontinue treatment.	

[a] Subjects requiring a delay of > 4 weeks should go off protocol therapy

[b] If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion.

[c] Subjects requiring > 2 dose level reductions should go off protocol therapy

6.3 Other Regorafenib-Related Grade 3 or 4 Non-Hematologic Toxicities

The dose reduction guidelines for non-hematologic toxicities are shown in Table 6. If a Grade 3 non-hematologic toxicity that is expected to be manageable and reversible with dose reduction occurs, treatment with regorafenib should be held until the toxicity resolves to ≤ Grade 1. If the Grade 3 non-hematologic toxicity lasts longer than 7 days, study drug will be discontinued. Patients with Grade 3 non-hematologic toxicity lasting ≥ 7 days that does not resolve to ≤ Grade 1 within 3 weeks should also be removed from the study, unless the treating physician and the Medical Monitor agree that continued treatment at lower doses is in the best interest of the patient. If a Grade 4 non-hematologic toxicity occurs, study drug will be discontinued.

If Grade 3 or 4 non-hematologic toxicity other than nausea, vomiting, or alopecia occurs, treatment with regorafenib should be held, and should be resumed at 1-level dose reduction(s) (see Table 1) as soon as the toxicity resolves to ≤ Grade 1. Dose reductions will also apply for nausea and vomiting if the toxicity is Grade 3 or 4 and persists for 7 days after maximal antiemetic prophylaxis.

Table 6 Dose Modifications for Regorafenib Non-Hematologic Toxicities

Toxicity	Regorafenib Dose[a]
Grade 1 and Grade 2	No dose modifications[a].
Grade 3[b]	Hold dose until recovery to ≤ Grade 2 (for AEs in Cycle 1: resolution to ≤ Grade 1), then resume regorafenib at one lower dose level. For AEs occurring in Cycle 2 or later the investigator may consider a retreatment at the dose Level 0. If subject experiences a second Grade 3 toxicity, withhold dose until toxicity is ≤ Grade 2, then reduce 1 dose level and resume treatment.
Grade 4[b]	Discontinue treatment. For certain toxicities such as laboratory assessments (e.g., lipase increase without signs of a clinical pancreatitis), a decision about the further continuation and dose of treatment has to be determined after discussion between investigator and the sponsor.

[a]The investigator may consider lowering the regorafenib dose level in the case of Grade 1-2 toxicities which interfere with the activities of daily life, such as long lasting fatigue, anorexia, etc.

[b]Subjects who develop Grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, or Grade 3/Grade 4 hypophosphatemia may continue study treatment without interruption if this is deemed medically acceptable by the investigator. Relevant diagnostic measures to exclude other adverse events leading to hyperlipasemia, hyperamylasemia, or hypophosphatemia will be mandatory before dosing of regorafenib is continued.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedules of Assessments for the two cohorts in this study are shown in Appendix A **Error! Reference source not found.** and Appendix B**Error! Reference source not found.**.

Informed consent must be obtained ≤28 days prior to initiation of treatment and before any protocol-specific procedures are performed. The Screening physical examination, medical history, ECOG PS, complete blood counts (CBC), differential and platelets, comprehensive metabolic profile (CMP), and prothrombin time/partial thromboplastin time/international normalized ratio (PT/PTT/INR) should be done ≤21 days prior to initiation of treatment. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. CT scan of the chest, abdomen, and pelvis should be performed ≤28 days prior to initiation of treatment, as should a carcinoembryonic antigen (CEA) tumor marker.

Cohort 1 and Cohort 2 patients will be assessed to determine suitability for SIR-Spheres. These assessment tests will be obtained 7-4 days prior to SIR-Spheres treatment. Cohort 1 patients will have these assessments performed during week 4 prior to SIR-spheres treatment. Cohort 2 patients will be assessed at Screening.

Patients need to fast for 6 hours before receiving SIR-Spheres treatment.

Imaging studies to be submitted for central review are listed in Section 13.3.

7.2 Patient Assessment for SIR-Spheres

Cohort 1 and Cohort 2 patients will be assessed to determine suitability for SIR-Spheres.

The following tests will be obtained 7-4 days prior to SIR-Spheres treatment.

- **Hepatic angiogram**
- **^{99m}Tc MAA lung shunt scan**

Cohort 1 patients will have these assessments performed during week 4 prior to SIR-spheres treatment.

Cohort 2 patients will be at assessed at Screening 7-4 days prior to SIR-Spheres treatment on CID1.

7.3 Study Treatment Assessments - COHORT 1

7.3.1 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at Screening ≤21 days prior to initiation of treatment unless otherwise noted:

- Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)
- Medical history

- Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, respiratory rate, and oral temperature)
- Blood pressure (BP)
- ECOG PS (Appendix D)
- Concomitant medication review
- CBC (complete blood count) including hemoglobin, hematocrit, white blood cell (WBC) with 3-part differential, and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin plus lactate dehydrogenase (LDH), and phosphorus.
- PT/PTT/INR
- Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)
- Disease assessments:
    - CT scan chest, abdomen, and pelvis (≤ 28 days prior to treatment)
    - CEA tumor marker

7.3.2 Cycle 1, Day 1

If the following are performed within 72 hours of Cycle 1 Day 1 they do not have to be repeated:

- Medical history
- Physical examination, measurements of weight, and vital signs (resting heart rate, respiratory rate, and oral temperature)
- BP
- ECOG PS
- Concomitant medication review
- CBC
- CMP
- PT/PTT/INR
- Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)
- CEA tumor marker

7.3.3 Cycle 1, Day 8 and 15

- Physical examination, weight, and vital signs
- BP
- ECOG PS
- AE assessment
- Concomitant medication review
- CBC
- CMP
- PT/PTT/INR (for patients receiving Coumadin therapy)

7.3.4 Cycle 1, Day 22 (assessments to be completed ≤7 days prior to SIR-Spheres treatment)

- Physical examination, weight, and vital signs
- BP
- ECOG PS
- AE assessment
- Concomitant medication review
- CBC
- CMP
- PT/PTT/INR (for patients receiving Coumadin therapy)
- Biomarker blood sample collection prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan
- CEA tumor marker

The following tests will be obtained 7-4 days prior to SIR-Spheres treatment:

- Hepatic angiogram
- ^{99m}Tc MAA lung shunt scan

7.3.5 Cycle 2, Day 1

SIR-Spheres may not be administered until the patient's hematologic, liver and renal function assessments performed per Section 7.3.4 have been re-confirmed as eligible according to Section 3.1 by the Investigator.

- SIR-Spheres treatment
- BP

7.3.6 Cycle 2, Day 8

- BP
- AE assessment
- CMP
- Biomarker blood sample collection (following SIR-Spheres treatment)

7.3.7 Cycle 3 and Beyond, Day 1 (±72 hours)

Regorafenib may not start until the patient's hematologic, liver and renal functions have been re-confirmed as eligible according to the Section 3.1 by the Investigator. Therefore, the regorafenib cycle starts on the day that treatment begins. If liver function toxicities are present, patient may be rechecked weekly for 2 additional weeks. Those patients with persistent liver function toxicities after this time will come off study, but will be followed until resolution.

- Physical examination, weight, and vital signs
- BP
- ECOG PS
- AE assessment
- Concomitant medication review
- CBC
- CMP
- PT/PTT/INR (for patients receiving Coumadin therapy)
- Biomarker blood sample collection (Day 30 (pre-dose) following SIR-Spheres treatment)
- CEA tumor marker

7.3.8 Cycle 3 and Beyond, Day 15

- PT/PTT/INR (for patients receiving Coumadin therapy)

7.4 Study Treatment Assessments – COHORT 2

7.4.1 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at Screening ≤21 days prior to initiation of treatment unless otherwise noted. The following must be repeated or performed ≤7 days of Cycle 1 Day 1 to document Cycle 1 Day 1 assessments prior to SIR-Spheres treatment unless otherwise noted:

- Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)
- Medical history
- Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, respiratory rate, and oral temperature)
- Blood pressure (BP)
- ECOG PS (Appendix D)
- Concomitant medication review
- CBC (complete blood count) including hemoglobin, hematocrit, white blood cell (WBC) with 3-part differential, and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin plus lactate dehydrogenase (LDH), and phosphorus.
- PT/PTT/INR
- Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)
- Biomarker blood sample collection prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, which will be obtained 7-4 days prior to SIR-Spheres treatment
- Disease assessments:
    - CT scan chest, abdomen, and pelvis (≤ 28 days prior to treatment)
    - CEA tumor marker

7.4.2 Cycle 1, Day 1

- SIR-Spheres treatment

7.4.3 Cycle 1, Day 8

- AE assessment
- CMP
- Biomarker blood sample collection (following SIR-Spheres treatment)

7.4.4 Cycle 2, Day 1 (±72 hours)

Regorafenib may not start until the patient's hematologic, liver and renal functions have been re-confirmed as eligible according to Section 3.1 by the Investigator. Therefore, the regorafenib cycle starts on the day that treatment begins. If liver function toxicities are present, patient may be rechecked weekly for 2 additional weeks. Those patients with persistent liver function toxicities after this time will come off study, but will be followed until resolution.

- Physical examination, weight, and vital signs
- BP
- ECOG PS
- AE assessment
- Concomitant medication review
- CBC
- CMP
- PT/PTT/INR (for patients receiving Coumadin therapy)
- CEA tumor marker
- Biomarker blood sample collection (Day 30 following SIR-Spheres treatment only)

7.4.5 Cycle 2, Day 8 and 15

- Physical examination, weight, and vital signs
- BP
- ECOG PS
- AE assessment
- Concomitant medication review
- CBC
- CMP
- PT/PTT/INR (for patients receiving Coumadin therapy)

7.4.6 Cycle 2, Day 22

- BP

7.4.7 Cycle 3 and Beyond, Day 1 (±72 hours)

- Physical examination, weight, and vital signs
- BP
- ECOG PS
- AE assessment
- Concomitant medication review
- CBC

- CMP
- PT/PTT/INR (for patients receiving Coumadin therapy)
- CEA tumor marker

7.4.8 Cycle 3, Day 8

- BP

7.4.9 Cycle 3 and Beyond, Day 15

- PT/PTT/INR (for patients receiving Coumadin therapy)

7.5 Response Assessment Week 6 and Week 12 after SIR-Spheres, and then every 8 Weeks

Patients will be reassessed for response according to RECIST v1.1 (Appendix C) at Weeks 6 and 12 after SIR-Spheres with CT scans in both cohorts. After completing SIR-Spheres and 2 cycles of regorafenib patients may continue regorafenib treatment alone, if tumor response is stable or better. Patients continuing treatment after Week 12 will have response re-assessed at 8-week intervals (±1 week). Patients with progressive disease (PD) or unacceptable toxicity will be discontinued from the study.

The following assessment will be performed:

- CT scan of chest, abdomen, and pelvis. If CT chest is normal at baseline this does not have to be repeated with each restaging unless there is a clinical reason to do so. If a CT scan is not possible, then an MRI may be used.

As noted above in the Day 1 assessments for all cycles, CEA tumor markers must be assessed on Day 1 of each cycle and at the End-of-Treatment visit.

7.6 End-of-Treatment Visit

Patients are permitted to continue treatment with regorafenib until disease progression, or the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician.

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End-of-Treatment visit.

After withdrawal from or completion of protocol treatment, patients must be followed for any new AEs for 30 calendar days after the last dose of study drug.

The following end-of-treatment visit procedures will be performed.

- Physical examination, weight, and vital signs
- BP
- ECOG PS

- AE assessment
- Concomitant medication review
- CBC
- CMP
- PT/PTT/INR (for patients receiving Coumadin therapy)
- Disease assessment
    - CT scan of chest, abdomen and pelvis
    - CEA tumor marker

7.7 Follow-Up

7.7.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

Patients discontinuing treatment for any reason other than PD will be monitored for evidence of disease progression. Patients will be followed every 3 months (±1 month) for up to a maximum of 6 months after the last patient has been enrolled on study for disease progression. Assessments at these visits will be performed as described in Appendix A **Error! Reference source not found.** and Appendix B**Error! Reference source not found.**.

7.7.2 Survival Follow-Up

After disease progression is documented, patients will be followed every 3 months (±1 month) for survival (e.g., date and cause of death) for up to a maximum of 6 months after the last patient has enrolled on study or death whichever comes first. Patients may be contacted during outpatient visits or by telephone.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 SIR-Spheres® Microspheres

SIR-Spheres microspheres are to be administered in accordance with the terms of its marketing authorization and in accordance with institutional standard of practice. Please refer to the US Package Insert http://www.sirtex.com/us/clinicians/package-insert for detailed information on how to prepare and administer SIR-Spheres microspheres.

8.1.1 Labeling, Packaging, and Supply

Each site will procure a supply of SIR-Spheres microspheres, which is commercially available.

All study medications must be kept in a secure place under appropriate storage conditions. Storage conditions for SIR-Spheres microspheres can be found in the relevant US Package Insert. The expiration date on the label must not be exceeded.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of SIR-Spheres® Microspheres

SIR-Spheres microspheres should be prepared and administered in accordance with the terms of its marketing authorization. .

8.1.3 Precautions and Risks Associated with SIR-Spheres® Microspheres

Overall, the incidence of complications after SIR-Spheres microspheres therapy, if patients are selected appropriately and target (i.e. liver) delivery is performed meticulously, is low. Gastroduodenal complications occur in less than 10% of those treated (Bester et al. 2011; Kennedy et al. 2006;Stubbs et al. 2004) and are largely preventable.

A life-threatening complication, progressive pulmonary insufficiency secondary to radiation-induced lung fibrosis can be avoided by excluding from treatment with SIR-Spheres microspheres any patient with marked hepato-pulmonary shunting (Leung et al. 1995). There have been rare reported occurrences of this complication since that time.

The gallbladder also may receive SIR-Spheres microspheres through a patent cystic artery leading to radiation cholecystitis. In order to avoid this potential complication, infusion distal to the cystic artery is preferred, however the risk of radiation cholecystitis requiring cholecystectomy is low (Liu et al. 2005).

Gastric and duodenal ulceration have been reported to occur after the use of SIR-Spheres microspheres and are related to the inadvertent intestinal deposition of microspheres via extra-hepatic visceral arterial branches. Even in the absence of extra-hepatic activity on ^{99m}Tc labelled MAA and Bremsstrahlung emission images, gastrointestinal symptoms have been reported to develop. The risk of gastrointestinal ulceration can be minimised with routine coil embolization of the extra-hepatic visceral arteries before infusion of SIR-Spheres microspheres (Liu et al. 2005).

Radioembolization induced liver disease (REILD) is a rare complication following selective internal radiation therapy (SIRT) with ^{90}Y microspheres. REILD is characterised by a well-defined constellation of temporal, clinical, biochemical and histopathologic findings. REILD typically manifests approximately 4-8 weeks post-SIRT and is characterised clinically by jaundice and ascites in the absence of tumour progression or bile duct obstruction. The typical biochemical picture of REILD is an elevated bilirubin (> 3mg/dL) in almost all cases, elevated ALP and gamma-glutamyl transpeptidase (GGT) in most cases, accompanied by virtually no change in the transaminases (AST and ALT) In the event that a liver biopsy is performed, the typical histological appearance is of sinusoidal obstruction that may resemble veno-occlusive disease.

REILD may occur in both non-cirrhotic and cirrhotic patients. In non-cirrhotic patients, the main risk factors for the development of REILD include prior exposure to systemic chemotherapy and whole-liver SIRT. In cirrhotic patients, the main risk factors are small liver volume (<1.5 L) and elevated bilirubin (1.2 mg/dL) at baseline. It is relevant to note that REILD is indeed very rare in the setting of an otherwise healthy liver and is largely confined to patients with a well-known

liver condition such as cirrhosis or who have been exposed to any form of potential liver insult, most usually prior chemotherapy. Patients presenting with small liver volumes (< 2.0 L) and low proportional tumour burden (< 0.20) may be at higher risk of developing REILD independent of other factors; appropriate dose recommendations per the study protocol should be strictly adhered to in these cases.

The treatment of REILD may comprise tapering high dose corticosteroids and ursodeoxicolic acid. Low molecular weight heparin may also be considered but both corticosteroids and heparin may only be useful if commenced very early in the course of the disease.

Apart from the above listed major complications[2] other side effects and complications include:

In approximately one-third of patients, administration of SIRT causes immediate short term abdominal pain requiring narcotic analgesia.

Post SIRT treatment lethargy and mild nausea are common symptoms and can last up to ten days and may require medication.

Most patients develop a mild fever that may last for several days following SIRT administration. This fever does not require treatment.

The most common potential serious complications result from either (1) inadvertent administration of SIR-Spheres microspheres into the gut resulting in gastritis/duodenitis or (2) radiation induced liver disease resulting from a radiation overdose to the normal liver parenchyma. The incidence rate of gastritis/duodenitis can be reduced by experience and meticulous attention to the administration procedure so as to ensure that there is a minimal chance of SIR-Spheres microspheres entering small arteries supplying the gut. Radiation induced liver disease is largely, but not totally, preventable by using correct SIR-Spheres microspheres doses and making allowances for dose reduction when there is increased risk of causing radiation damage such as in pre-existing liver damage, poor liver reserve or small volume tumour mass in the liver. The reported incidence of gastritis/duodenitis is <10%, while the reported rate of radiation induced liver disease is < 1%.

Rare complications that have been reported include acute pancreatitis resulting from SIR-Spheres microspheres refluxing back down the hepatic artery and lodging in the pancreas and liver abscess from infection of necrotic tumour. Previously reported radiation pneumonitis has not been observed where appropriate treatment workup and dose reductions are followed.

There is some evidence that there is a decrease in leucocyte levels, with a nadir eight weeks after implantation. This has been evident in both first line and refractory studies.The median number of leukocytes was 3.55 x 10^9/L (NCIC CTC3 Grade 1). Leukocyte levels recover from this point, with the median value rising to normal levels 4-8 weeks after the decline.

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[2] Unpublished data, Sirtex Technology Pty Ltd

Please refer to the US Package Insert for detailed information on the risks associated with the use of SIR-Spheres microspheres.

8.2 Regorafenib

Regorafenib is to be administered in accordance with the recommendations in the approved labelling and in accordance with institutional standard of practice. Please refer to the US Package Insert http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf for detailed information on how to prepare and administer Regorafenib.

8.2.1 Labeling, Packaging, and Supply

Regorafenib is commercially available and will be purchased by the patient or a third party.

8.2.2 Preparation and Administration of Regorafenib

A link to the full US Package Insert is provided in Section 8.2.

8.2.3 Precautions and Risks Associated with Regorafenib

Please refer to the US Package Insert for detailed information on the risks associated with the use of Regorafenib.

8.2.3.1 In-Vitro Radiosensitization Study of Regorafenib and Radiation in Adenocarinoma Cell Lines

The radiosensitization of the Regorafenib / radiotherapy combination was evaluated in adenocarcinoma cell lines. The purpose of the study was to determine the extent to which Regorafenib would potentiate the tumoricidal effect of radiation. Colorectal adenocarcinoma cell lines were subjected to selected combinations of regorafenib concentrations and exposure to radiation. The addition of regorafenib to radiation did not enhance radiosensitization irrespective of the timing or temporal sequencing of the two agents. Moreover, there was no dose-dependent relationship observed in the radiosensitization of cancer cell lines. Based on the results of this study, Regorafenib is not an intrinsic radiosensitizer in colorectal cancer cells. A detailed report of study findings is included in Appendix H.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (see Appendix C). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

The safety of two treatment cohorts will be evaluated in this open-label study. The administration sequence of radioembolization with SIR-Spheres and regorafenib is different in the two treatment cohorts. The treatment cohorts are:

Cohort 1 Regorafenib (one cycle) followed by SIR-Spheres followed by re-initiation of regorafenib 2-4 weeks after SIR-Spheres

Cohort 2 SIR-Spheres followed by regorafenib to start 2-4 weeks after SIR-Spheres

Enrollment to Cohort 1 will be completed before Cohort 2 begins enrolling patients. All patients will take regorafenib, orally once-a-day, on Days 1-21 of a 28-day treatment cycle. Twenty-five patients will be treated in each cohort.

Primary Objective

The primary objective of the study is to evaluate the safety of two treatment cohorts combining regorafenib and SIR-Spheres in patients with refractory mCRC with liver metastasis.

Secondary Objectives

The secondary objectives of the study are to evaluate the overall response rate (ORR), progression free survival (PFS), and OS of patients with refractory mCRC when treated with combination SIR-Spheres and regorafenib in the two sequencing cohorts.

Exploratory Objectives

The exploratory objectives will evaluate the status of biomarkers and correlate the clinical outcomes of patients treated in the two SIR-Spheres and regorafenib cohorts.

10.2 Sample Size Considerations

There is no formal hypothesis testing in this study. The sample size of 50 patients (25 in each cohort) is based on clinical practicalities rather than statistical reasoning, in order to evaluate the safety of the 2 different sequences in treatment administration of SIR-Spheres microspheres and regorafenib.

With 25 patients per cohort, the 95% confidence interval for the response rate estimate would be no more than 21%.

10.3 Analysis Population

The following analysis populations will be used:

- Intent-To-Treat Population (ITT) is defined as all patients who have started study treatment (Radioembolization with SIR-Spheres ^{90}Y or regorafenib).
- Safety Population is defined as all patients who have received at least one dose of study treatment. In this instance, the ITT and safety populations would consist of the same patients.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to events endpoints will be reported using Kaplan-Meier estimates, with 95% confidence intervals for median time to event.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized for each cohort. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, treated, completed the treatment/study and withdrawn from treatment/study for any reasons will be presented overall and also by cohort.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Intent-To-Treat Population.

- Overall Response Rate (ORR) is defined as the proportion of patients with observed CR or PR (i.e. 2 CRs or PRs at least 4 weeks apart) according to the RECIST 1.1 criteria.

- Progression Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the RECIST v1.1 criteria, or death on study. Patients who are alive and free from disease progression will be censored at the date of last adequate tumor assessment.

- Overall Survival (OS), defined as the time from the first day of study drug administration (Day 1) to death. Patients who are alive will be censored at the date of last known date alive.

For ORR, the estimates and the associated 95% confidence interval (based on the Clopper-Pearson method) in each treatment group will be calculated.

For PFS and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% confidence interval will be provided.

10.4.3 Early Safety Monitoring and Stopping Rules

A safety review for toxicity by the Medical Monitor will occur after the first 10 patients have been enrolled in each cohort and treated with one cycle of regorafenib and SIR-spheres (combination therapy) to assess the frequency of ≥ Grade 3 adverse events and all SAEs. Accrual will not be halted while the analysis is being conducted.

Stopping Rules Due to Toxicities of Combination Therapy

Stopping rules due to toxicities assessed as related to combination therapy by the Medical Monitor will be defined as follows:

- A patient death considered to be caused by AEs of combination therapy

- A patient with Grade 4 AST, ALT, or irreversible hepatic failure assessed as related to combination therapy;
- More than 2 patients that develop Grade 3 AST, ALT, or total bilirubin assessed as related to combination therapy;
- More than 2 patients develop Grade 3 bleeding in the lung, stomach, small intestine, or liver assessed as related to combination therapy.

If the early stopping rules are met or safety signals emerge from the group of the first 10 patients treated with combination therapy in each cohort, patient recruitment will discontinue and the study will be reassessed. Any outcome of these safety reviews will be communicated in a timely manner to the participating investigators so that they may notify their IRBs.

10.4.4 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v 4.03 A copy of CTCAE scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. AEs that occur prior to initiation of therapy (after consent is signed, i.e. during mapping for SIR-Spheres treatment), will also be assessed.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term by cohort for all patients in the Safety Population. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented by treatment cohort.

Other safety endpoints including laboratory results will be summarized for all patients in the Safety Population.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary and they will be listed and summarized by treatment cohort.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur 6 months after the last patient has been recruited into the study.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and Serious AEs (SAEs), measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting AEs to the SCRI Innovations Safety Department (see Section 11.2). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- **Death**
- **A life-threatening AE (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)**
- **Inpatient hospitalization or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory

reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to the study material or process (i.e., whether the event is related or unrelated to study drug administration, SIR-Spheres microspheres or SIRT procedure).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a serious adverse event (SAE) or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.0, and changes will be documented.

If the AE is serious, it should be reported immediately to SCRI Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to regorafenib and/or SIR-Spheres treatment (called study treatment), spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Unrelated:	No relationship between the experience and the administration of study device or drug; related to other etiologies such as concomitant medications or patient's clinical state.
Unlikely:	The current state of knowledge indicates that a relationship is unlikely.
Possibly Related:	A reaction that follows a plausible temporal sequence from administration of the study device or drug and follows a known response pattern to the suspected study material. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Probably Related:	A reaction that follows a plausible temporal sequence from administration of the study device or drug and follows a known response pattern to the suspected study material. The reaction cannot be reasonably explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
Definite:	There is a definite relationship between the experience and the administration of study device or drug.

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to SCRI Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through the 30 day period after the last dose of study drug. **The SCRI Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to SCRI Innovations Safety Department via fax or e-mail using the using the following contact information (during both business and non-business hours):

SCRI Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@scri-innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations Safety Department as soon as it is available; these reports should be submitted using the SCRI Innovations SAE Report Form.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room

- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as a SAE to the SCRI Innovations Safety Department.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the SCRI Innovations Safety Department. SCRI Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the SCRI Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 Study Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the SCRI Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of the study drug, see the Package Insert.

11.4 Sponsor Serious Adverse Event Reporting Requirements

SCRI Innovations Safety Department will forward SAE information to Sirtex Medical within 1 business day of SCRI Innovations Safety Department personnel becoming aware of the SAE.

Sirtex Medical

Jo Fladger

Phone: 781-721-3844

Fax: 877-221-0256

Email: jfladger@sirtex.com

SCRI Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, and FDA regulations 21CFR parts 312, 812.140, 812.46.

Sirtex Medical is responsible for determining reportablity of SAEs that a device has or may have caused or contributed to a death or serious injuries under the MDR (Medical Device Reporting) 21CFR Part 803. Within 72 hours of receipt, Sirtex Medical will determine the relationship between the SAE and the device and they will notify the SCRI Innovations Safety Department. SCRI Innovations Safety Department will complete the SAE report to the relevant regulatory authorities.

11.4.1 Sponsor Assessment of Unexpected Drug Events

The Sponsor is responsible for assessing an adverse event or suspected adverse event as "unexpected".

An adverse event or suspected adverse reaction is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert)
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application

- Includes AEs or SARs that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected adverse event may also apply to an event that is not listed in the current US Package Insert (USPI) or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the Investigator's Brochure or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the USPI or current IB.

11.4.2 Sponsor Reporting for Clinical Studies Under an Investigational Device Exemption

All written IDE Safety Reports submitted to the FDA by the SCRI Innovations Safety Department must also be faxed to the company(ies) that are supporting the study:

Sirtex Pty Ltd

Fax: 877-221-0256

11.4.3 Sponsor Assessment of Unexpected Adverse Device Effects

Any events determined by the PI to be unanticipated adverse device effects will be reported to the SCRI Innovations Safety Department as soon as possible but not more than 10 working days after the investigator first learns of the effect. These unanticipated adverse device effects will be reported to the reviewing IRB, the FDA, and the study team as soon as possible but not more than 10 working days after the investigator first learns of the effect.

Any unanticipated adverse device effect will be immediately evaluated by the Sponsor-investigator. Should it be determined the unanticipated adverse device effect presents an unreasonable risk to study subjects, the study or the part(s) of the study that presents that risk will be terminated as soon as possible but not later than 5 working days after the Sponsor-investigator first receives notice of the effect.

12. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice (GCP) outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

12.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), package inserts, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for study drugs, will be prepared by the Sponsor or its representative as required, for distribution to the investigator(s) and submission to the relevant IRB.

12.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

12.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

12.3.1 Confidentiality

12.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

12.3.1.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

12.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the SCRI Innovations and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54.6 and 812.43 shall be appropriately provided.

13. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

13.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representative. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and/or FDA or other regulatory authority's approval which include but are not limited to the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

13.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list, if provided
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- A signed Investigator agreement and curricula vitae (CVs) of participating investigators
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of SCRI Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure information for all investigators listed in the Investigator's agreement (if applicable)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

13.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The following imaging studies will be submitted for central review when available:

1. CT/MRI and SPECT MAA study (DICOM) used to calculate ^{90}Y activity prescription used to treat patient. Patient identifiers must be removed and replaced by the patient's unique trial number.
2. Bremsstrahlung SPECT study (DICOM) obtained after ^{90}Y treatment. Patient identifiers must be removed and replaced by the patient's unique trial number.

3. CT/MRI studies (DICOM) obtained at 6 & 12 weeks post ^{90}Y as per protocol follow up. Patient identifiers must be removed and replaced by the patient's unique trial number.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8, 21 CFR Part 312.57, and Part 812.140, including key documents such as the IB and any amendments, protocol and any amendments signed ICFs, copies of completed CRFs, IRB approval documents, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6, Part 812.43 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 and Part 812.140 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRF records, and medical records), all original, signed ICFs, and copies of all eCRF records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even

if retention requirements have been met. All study files will be maintained by the Sponsor throughout the study, and will be transferred to the Sponsor at the conclusion of the study.

13.4 Data Collection

The study eCRFs are the primary data collection instrument for the study. Electronic case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF system must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will review and electronically sign and date each patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

13.5 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB and the Sponsor or its representative(s).

13.6 Quality Assurance and Quality Control

Each study site shall be required to have Standard Operating Procedures to define and ensure quality assurance/control processes for study conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13.7 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication strategy.

Inclusion of the investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any SCRI Innovations Confidential Information from all publications.

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15. APPENDICES

Appendix A: Schedule of Assessments – Cohort 1- Regorafenib then SIR-Spheres then Regorafenib

Procedures	Screening	Cohort 1 –Regorafenib then SIR-Spheres then Regorafenib									End of Treatment Visit[l]	Follow-Up	
		Regorafenib				SIR-Spheres		Regorafenib				Disease-Free Survival[m]	Survival[n]
		Cycle 1				Cycle 2		Cycle 3 and Beyond					
		Days				Days		Days					
	Baseline[b]	1[b]	8	15	22[q]	1	8	1	8	15			
TESTS & OBSERVATIONS													
Informed Consent[a]	X[a]												
Medical history	X	X											
Physical examination, vital signs, height, weight[c]	X	X	X	X	X			X			X	X	
Blood Pressure	X	X	X	X	X	X	X	X			X	X	
ECOG Performance Status	X	X	X	X	X			X			X	X	
Adverse event evaluation			X	X	X		X	X			X	X	
Concomitant medication review	X	X	X	X	X			X			X	X	
Survival Status													X
LABORATORY TESTS													
CBC, including differential and platelets[d]	X	X	X	X	X			X			X	X	
CMP[e]	X	X	X	X	X		X	X[f]			X	X	
PT/PTT/INR[g]	X	X	X	X	X			X		X	X	X	
Serum or urine pregnancy test[i]	X	X											
Biomarker blood sample collection					X[h]		X[h]	X[h] (day 30)					

Appendix A: Schedule of Assessments – Cohort 1- Regorafenib then SIR-Spheres then Regorafenib

Procedures	Screening	Cohort 1 –Regorafenib then SIR-Spheres then Regorafenib									End of Treatment Visit[l]	Follow-Up	
		Regorafenib				SIR-Spheres		Regorafenib				Disease-Free Survival[m]	Survival[n]
		Cycle 1				Cycle 2		Cycle 3 and Beyond					
		Days				Days		Days					
	Baseline[b]	1[b]	8	15	22[q]	1	8	1	8	15			
DISEASE ASSESSMENT													
CT scan of the chest, abdomen, pelvis[j,k]	X									X[J]	X[J]	X[J]	
Tumor marker (CEA)	X	X			X			X			X		
Hepatic angiogram					X[o]								
^{99m}Tc MAA lung shunt scan[o]					X[o]								
TREATMENT													
Regorafenib PO (Days 1-21)[p]		Days 1-21						Days 1-21					
SIR-Spheres						X							

Appendix A: Cohort 1 Schedule of Assessments (continued)

a. Informed Consent must be obtained ≤28 days prior to the initiation of study treatment.
b. The Screening physical examination, update of medical history, ECOG performance status, CBC, CMP, and PT/PTT/INR, and concomitant medication review should be done ≤21 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day1 they do not have to be repeated on Cycle 1 Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) and tumor marker (CEA) should be performed ≤28 days prior to initiation of treatment.
c. Physical examinations will include measurements of height (Screening visit only), weight and vital signs (resting heart rate, respiratory rate, oral temperature). Blood pressure should be monitored weekly for the first 6 weeks of regorafenib treatment and then every cycle, or more frequently, if clinically indicated.
d. Hematology parameters include the following laboratory tests: complete blood count including WBC with 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit and platelets.
e. CMP must include glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST, ALT, total bilirubin, total protein, and albumin plus LDH, phosphorus.
f. If liver function toxicities are present after a 2 week rest, then patients may be rechecked weekly for 2 additional weeks. Reinitiation of regorafenib must be delayed until appropriate resolution of liver function toxicities.
g. PT/PTT/INR will be monitored in patients receiving Coumadin on Days 1, 8 (Cycle 1 only) and 15 of each treatment cycle.
h. Biomarker samples (see Section 5.4) will be collected from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, which will be obtained 7-4 days prior to SIR-Spheres treatment (see Section 7.2) and on Day 8 after SIR-Spheres treatment and Day 30 (pre-dose) after SIR-Spheres treatment.
i. Serum or urine pregnancy tests are to be conducted in women of childbearing potential within 72 hours of C1D1.
j. CT scan of the chest, abdomen and pelvis will be obtained at baseline ≤28 days prior to the initiation of treatment. Assessments required the same day of SIR-Spheres administration can be obtained ≤7 days prior to SIR-Spheres treatment. Patients will be restaged on Week 6 and Week 12 after SIR-Spheres treatment according to RECIST v1.1. All assessments should be performed within 7 days of the schedule day of assessment. Patients with stable disease or better may continue treatment with regorafenib. CEA tumor markers must be assessed on Day 1 of each cycle and at the End of Treatment visit.
k. Patients determined to have stable disease or better at the Week 12 restaging continuing treatment will begin 28-day treatment cycles (21 days oral regorafenib followed by one week rest). Patients will then be re-assessed according to RECIST v1.1 criteria every 8 weeks.
l. All patients will undergo the End of Treatment visit assessments listed within 30 days after treatment ends due to completion of the planned study treatment period, or once a patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End of Treatment visit. After withdrawal from or completion of protocol treatment, patients must be followed for adverse events for 30 calendar days after the last dose of study drug.
m. Patients will be followed every 3 months (±1 month) for up to a maximum of 6 months after the last patient has enrolled on study for toxicity and disease progression.
n. After disease progression is documented, patients will be followed every 3 months (±1 month) for survival (e.g., date and cause of death) for up to a maximum of 6 months after the last patient has enrolled on study or death whichever comes first. Patients may be contacted during outpatient visits or by telephone.
o. Patients will be at assessed 7-4 days prior to SIR-Spheres treatment to determine the suitability for SIR-Spheres (see Section 7.2).
p. Patients will self-administer regorafenib during Days 1-21.
q. The Cycle 1 Day 22 physical examination, ECOG performance status, CBC, CMP, and PT/PTT/INR, tumor marker (CEA), adverse event evaluation, and concomitant medication review to be completed ≤7 days prior to SIR-Spheres radiation treatment.

Appendix B: Schedule of Assessments - Cohort 2-SIR-Spheres then Regorafenib

Procedures	Screening	Cohort 2 – SIR-Spheres then Regorafenib									End of Treatment Visit[l]	Follow-Up	
		SIR-Spheres		Regorafenib									
		Cycle 1		Cycle 2				Cycle 3 and Beyond				Disease-Free Survival[m]	Survival[n]
		Days		Days				Days					
	Baseline[b]	1	8	1	8	15	22	1	8	15			
TESTS & OBSERVATIONS													
Informed Consent[a]	X[a]												
Medical history	X												
Physical examination, vital signs, height, weight[c]	X			X	X	X		X			X	X	
Blood Pressure	X			X	X	X	X	X	X[p]		X	X	
ECOG Performance Status	X			X	X	X		X			X	X	
Adverse event evaluation			X	X	X	X		X			X	X	
Concomitant medication review	X			X	X	X		X			X	X	
Survival Status													X
LABORATORY TESTS													
CBC, including differential and platelets[d]	X			X	X	X		X			X	X	
CMP[e]	X		X	X[f]	X	X		X			X	X	
PT/PTT/INR[g]	X			X	X	X		X		X	X	X	
Serum or urine pregnancy test	X[i]												
Biomarker blood sample collection	X[h]		X[h]	X[h] (day 30)									

Appendix B: Schedule of Assessments - Cohort 2-SIR-Spheres then Regorafenib (continued)

Procedures	Screening	Cohort 2 – SIR-Spheres then Regorafenib									End of Treatment Visit[l]	Follow-Up	
		SIR-Spheres		Regorafenib								Disease-Free Survival[m]	Survival[n]
		Cycle 1		Cycle 2				Cycle 3 and Beyond					
		Days		Days				Days					
	Baseline[b]	1	8	1	8	15	22	1	8	15			
DISEASE ASSESSMENT													
CT scan of the chest, abdomen, pelvis[j,k]	X					X[J]					X[J]	X[J]	
Tumor marker (CEA)	X			X				X			X		
Hepatic angiogram	X												
^{99m}Tc MAA lung shunt scan	X												
TREATMENT													
SIR-Spheres		X											
Regorafenib PO (Days 1-21)[o]				Days 1-21				Days 1-21					

Appendix B: Cohort 2 Schedule of Assessments (continued)

a. Informed Consent must be obtained ≤28 days prior to the initiation of study treatment.
b. The Screening physical examination, update of medical history, ECOG performance status, CBC, CMP, and PT/PTT/INR, concomitant medication review and tumor marker (CEA) should be done ≤21 days prior to initiation of treatment. These initial examinations must be repeated or performed ≤7 days of Cycle 1 Day 1 to document Cycle 1 Day 1 assessments prior to SIR-Spheres treatment. CT scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤28 days prior to initiation of treatment. Patients will be assessed at Screening (7-4 days prior to SIR-Spheres treatment) to determine the suitability for SIR-Spheres (see Section 7.2).
c. Physical examinations will include measurements of height (Screening visit only), weight and vital signs (resting heart rate, respiratory rate, oral temperature). Blood pressure should be monitored weekly for the first 6 weeks of regorafenib treatment and then every cycle, or more frequently, if clinically indicated.
d. Hematology parameters include the following laboratory tests: complete blood count including WBC with 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit and platelets.
e. CMP must include glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST, ALT, total bilirubin, total protein, and albumin plus LDH, phosphorus.
f. If liver function toxicities are present after a 2 week rest, then patients may be rechecked weekly for 2 additional weeks prior to Regorafenib treatment on C2D1. .
g. PT/PTT/INR will be monitored in patients receiving Coumadin on Days 1, 8 (Cycle 2 only), and 15 of each treatment cycle.
h. Biomarker samples (see Section 5.4) will be collected from all patients prior to the hepatic angiogram and ^{99m}Tc MAA lung shunt scan, which will be obtained 7-4 days prior to SIR-Spheres treatment [see Section 7.2]) and on Day 8 after SIR-Spheres treatment and Day 30 (pre-dose) after SIR-Spheres treatment.
i. Serum or urine pregnancy tests are to be conducted in women of childbearing potential within 72 hours of C1D1.
j. CT scan of the chest, abdomen and pelvis will be obtained at baseline ≤28 days prior to the initiation of treatment. Assessments required the same day of SIR-Spheres administration can be obtained ≤7 days prior to SIR-Spheres treatment. Patients will be restaged on Week 6 and Week 12 after SIR-Spheres treatment according to RECIST v1.1. All assessments should be performed within 7 days of the schedule day of assessment. Patients with stable disease or better may continue treatment with regorafenib. CEA tumor markers must be assessed on Day 1 of each cycle and at the End of Treatment visit.
k. Patients determined to have stable disease or better at the Week 12 restaging continuing treatment will begin 28-day treatment cycles (21 days oral regorafenib followed by one week rest). Patients will be re-assessed according to RECIST v1.1 criteria every 8 weeks.
l. All patients will undergo the End of Treatment visit assessments listed within 30 days after treatment ends due to completion of the planned study treatment period, or once a patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End of Treatment visit. After withdrawal from or completion of protocol treatment, patients must be followed for adverse events for 30 calendar days after the last dose of study drug.
m. Patients will be followed every 3 months (±1 month) for up to a maximum of 6 months after the last patient has enrolled on study for toxicity and disease progression.
n. After disease progression is documented, patients will be followed every 3 months (±1 month) for survival (e.g., date and cause of death) for up to a maximum of 6 months after the last patient has enrolled on study or death whichever comes first. Patients may be assessed during outpatient visits or contacted by telephone.
o. Patients will self-administer regorafenib during Days 1-21.
p. Blood pressure is required Cycle 3 Day 8. Cycle 4 and beyond, blood pressure will be required Day 1 only.

Appendix C: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Definitions

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <<10 mm or pathological lymph nodes with ≥10- to <<15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.

Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound:	When the primary study endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.

Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters..
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the subject also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

As detailed in Table 5 above, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for trials in which response rate is the primary endpoint, but is not required in randomized trials or trials with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the CRF.

Appendix D: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed << 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >> 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix E: Guidelines for Women of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 2 months after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected or implanted hormonal methods of contraception.

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 2 months after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to the SCRI Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to SCRI Innovations Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix F: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix G: Common CYP3A4 Inhibitors and Inducers

Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampicin
Nafcillin	Rofecoxib
Nevirapine	St. John's wort
Oxcarbazepine	Sulfadimidine
Phenobarbital	Sulfinpyrazone
Phenylbutazone	Troglitazone
Inhibitors	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Aprenavir	Mibefradil
Azithromycin	Miconazole
Bromocriptine	Nefazodone
Cannabinoids	Nelfinavir
Cimetidine	Nevirapine
Cisapride	Norfloxacin
Clarithromycin	Norfluoxetine
Clotrimazole	Omeprazole
Cyclosporine	Oxiconazole
Danazol	Paroxetine
Delavirdine	Propoxyphene
Dexamethasone	Quinidine
Diethyldithiocarbamate	Quinine
Diltiazem	Quinupristin and dalfopristin
Dirithromycin	Ranitidine
Disulfiram	Ritonavir
Entacapone (high dose)	Saquinavir
Erythromycin	Sertindole
Ethinyl estradiol	Sertraline
Fluconazole	Telithromycin
Fluoxetine	Troglitazone
Fluvoxamine	Troleandomycin
Gestodene	Valproic acid
Grapefruit juice	Verapamil
Indinavir	Zafirlukast
Isoniazid	Zileuton
Itraconazole	

Appendix H: Radiosensitization Study of Regorafenib and SIR-Spheres Microspheres

Interim Report for Sirtex Medical from University of Oxford

Screening of drugs to quantify radiosensitisation in cancer cell lines

Author: Dr R A Sharma, 6th August 2013

Description of the Project

This project aims to quantify the radiosensitisation exerted by drugs licensed for the treatment of metastatic colorectal cancer and hepatoma in a preclinical model system.

A cellular viability assay has been developed to screen drugs for the quantification of intrinsic radiosensitisation (RS) in a semi-automated high-throughput format. The assay has been validated against the current gold standard in cells grown in vitro, clonogenic survival assays. The principal benefit of the cellular viability assay over clonogenic survival assays is that the former can be used to study multiple permutations of dose, temporal sequencing and timing of radiotherapy relative to drug treatment, and a variety of drug concentrations, all in a significantly shorter timescale than the use of traditional methodology.

In the project proposed here, the principal investigator will demonstrate:

1. The degree of radiosensitisation affected by physiologically relevant concentrations of drugs licensed for treatment of colorectal cancer and hepatoma in cancer cell lines
2. The optimal temporal sequencing of each drug with radiotherapy
3. The most appropriate drug concentrations in cell lines to achieve optimal radiosensitisation.

Introduction

Colorectal cancer is the second most common cancer in the developed world (NCI 2010). Although approximately half of cases may be treated with surgery alone, for more advanced stage cancers, including metastatic disease, patient outcomes remain poor. Selective internal radiotherapy (SIRT) permits high doses of radiotherapy to be delivered safely to liver metastases from colorectal cancer. Primary liver cancer, hepatocellular carcinoma (HCC), is not responsive to traditional chemotherapy making it difficult to treat when inoperable. Improving radiotherapy treatment for HCC may benefit from the combinations of radiotherapy with radiosensitising drugs. Although various chemotherapeutics may be used as radiosensitisers, it is not currently clear which radiosensitising agents are most appropriate to improve clinical response rates.

In order to address this research deficit, we have developed a high-throughput assay for the identification of radiosensitising drugs to determine the most appropriate drugs to use with radiotherapy for specific cancers. Historically, screening programmes for intrinsic radiosensitisers have assessed anti-proliferative activity of compound libraries *in vitro* in 4-day assays (Lally *et al*. 2010), or have performed RNA interference to look at the effect of gene expression on response to radiotherapy (Higgins *et al.* 2010). Neither method permits high-throughput screening for radiosensitisers in a manner that directly correlates with the gold standard *in vitro*, i.e. clonogenic assays - where the ability of single cells to form colonies after irradiation is directly measured to enable comparison of radiosensitivity of drugs in different cell lines. Although it is the gold standard, clonogenic assays have major problems as the sole technique for assessing radiosensitivity. They suffer from time-consuming methodology (2 weeks for colony growth) and the expense (a large number of plates and large volumes of media and drugs are required to obtain a single survival curve). Moreover, low plating efficiency for some cell lines can also be problematic (e.g. HepG2 hepatoma cells, which are difficult to test with traditional clonogenic survival assays) and in some cases cannot be overcome. To facilitate the identification of radiosensitising drugs, we developed an assay and confirmed that it could be used as a valid surrogate for clonogenic survival *in vitro*. This assay was then extended robotically to screen compound libraries for potential radiosensitising agents.

Regorafenib is an oral multi-kinase inhibitor developed by Bayer which targets angiogenic, stromal and oncogenic receptor tyrosine kinase (RTK). Regorafenib shows antiangiogenic activity due to its dual targeted VEGFR2-TIE2 tyrosine kinase inhibition. We were asked by Sirtex to prioritise the testing of regorafenib in colorectal cancer cell lines with radiotherapy for this interim report.

Methods

Cell culture. Cell lines derived from colorectal adenocarcinoma (DLD1, RKO and HCT116) were cultured in Dulbecco's modified essential medium (DMEM) supplemented with 10% foetal calf serum, 1x non-essential amino acids and 1x Pen/Strep (Gibco). Cells were grown at 37ºC in a humidified incubator in 95% air with 5% CO_2 and passaged twice weekly. All experiments utilised exponentially growing cells with cell population doubling times of approximately 24 hours. Cell cultures were renewed after every 15 passages

Metabolic assays. Proliferation assays were used to optimise cell lines to measure the effects of drugs and/ or radiation. Cells were plated in serial dilutions on 96- or 384-well plates and treated with drugs and/ or radiation as appropriate. After 24 hours, media was refreshed and cells allowed to proliferate for 5-6 cell doubling times. As an indicator of cell proliferation after IR, metabolic activity in each well was measured using a coloured dye converted intracellularly into a yellow-fluorescing form. Cell culture media was replaced with DMEM containing 10 µg/ml dye. After 90 minutes, fluorescence was measured using a BMG Polarstar Optima plate reader.

Clonogenic survival assay. Cells were harvested, diluted to 10000 cells/ml and plated at appropriate cell numbers on 2 x 10 cm dishes/ radiation or drug dose. After 5-6 hours for cell attachment, cells were treated with regorafenib for the timescales stated in the figure legends, and irradiated with 0-8 Gy radiation using a 137-Cs source at a dose rate of ~2Gy/ min. Media were refreshed 24 hours after irradiation, and plates were incubated for 10-14 days. Colonies were stained with 0.4% methylene blue in 100% methanol for colony counting, and results were used to generate clonogenic survival curves.

The following permutations of combination treatment were tested by metabolic assay:

Cell line	Regorafenib concentration range	Timing of addition of drug tested
HCT116 (wild-type)	0 – 40 μM	24 hrs, 6 hrs and 1 hour **pre-**irradiation
HCT116 (wild-type)	0 – 40 μM	24 hrs, 6 hrs and 1 hour **post-** irradiation
HCT116 (KRAS mutant)	0 – 40 μM	24 hrs pre-irradiation
DLD1 (wild-type)	0 – 40 μM	24 hrs, 6 hrs and 1 hour **pre-**irradiation
DLD1 (wild-type)	0 – 40 μM	24 hrs, 6 hrs and 1 hour **post-** irradiation
DLD1 (KRAS mutant)	0 – 40 μM	24 hrs pre-irradiation
RKO (BRAF mutant)	0 – 40 μM	24 hrs pre-irradiation
RKO (BRAF wild-type)	0 – 40 μM	24 hrs pre-irradiation

Results

1. Measuring radiosensitivity

The metabolic assay was optimised to measure radiosensitivity of regorafenib under different sequencing conditions (drug added 24 h before RT, drug added at same time as RT and drug added 24 h after RT). The data obtained for DLD1 and HCT116 colorectal cancer cells are shown in Figures 1 and 2, which are typical of the results for all cell lines tested under all conditions and permutations. There was no dose-dependent radiosensitisation observed.

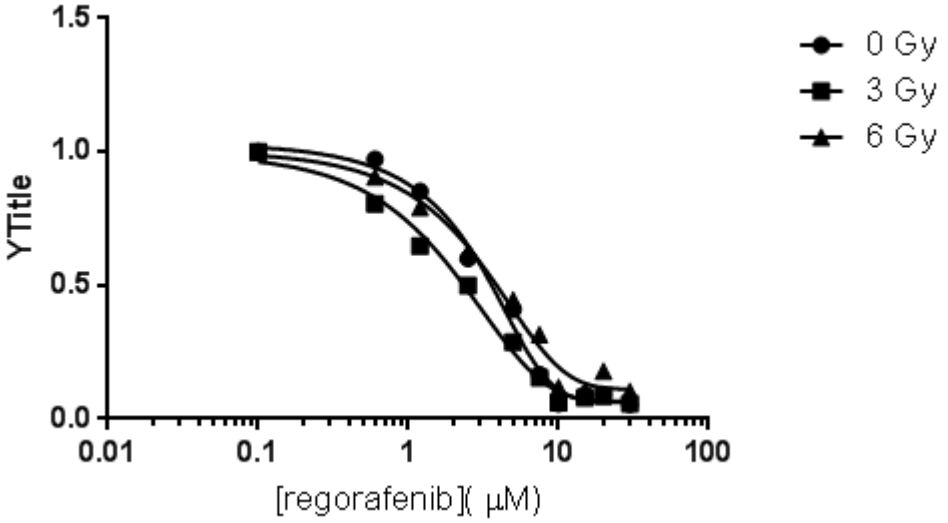


Figure 1

Figure 1. Regorafenib was added 24 h before radiotherapy treatment of DLD1 cells and cell proliferation measured by relative fluorescence obtained with dye on day 7 post-radiotherapy. There was no significant radiosensitisation observed. IC50 values for drug alone (0 Gy), drug + 3 Gy RT and drug + 6 Gy radiation were 3.2, 2.1 and 3.4 µM respectively (i.e. no significant difference without and with radiation).

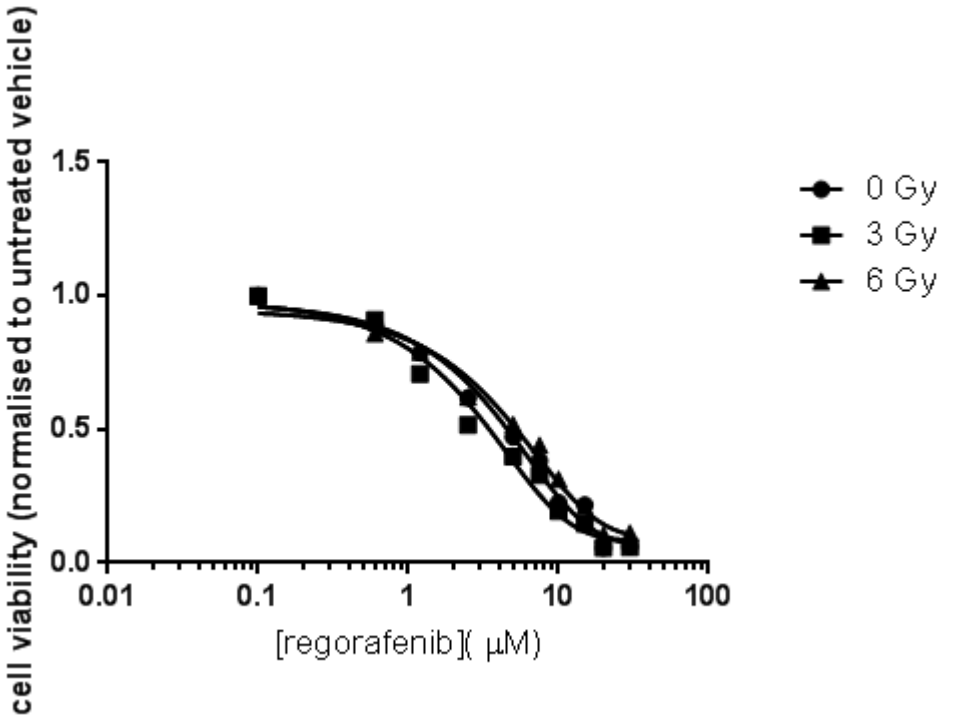
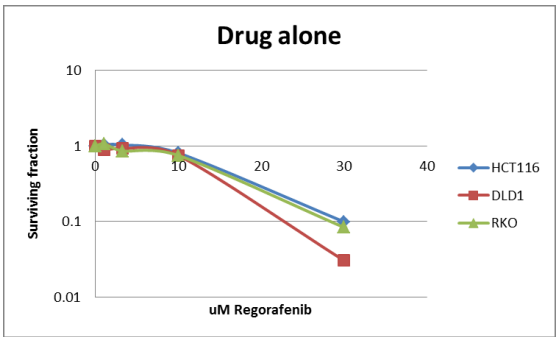


Figure 2

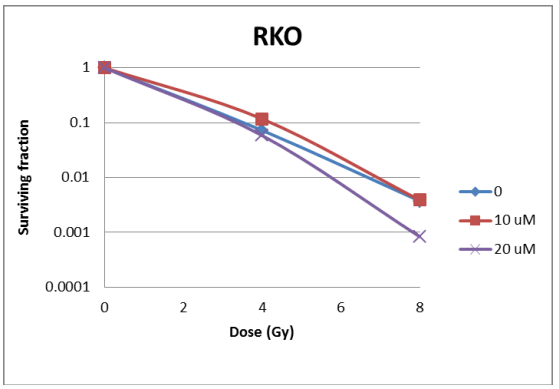
Figure 2. Regorafenib was added 24 h before radiotherapy treatment of HCT116 cells and cell proliferation measured by relative fluorescence obtained with dye on day 7 post-radiotherapy. There was no significant radiosensitisation observed.

2. Confirmation of results by clonogenic survival

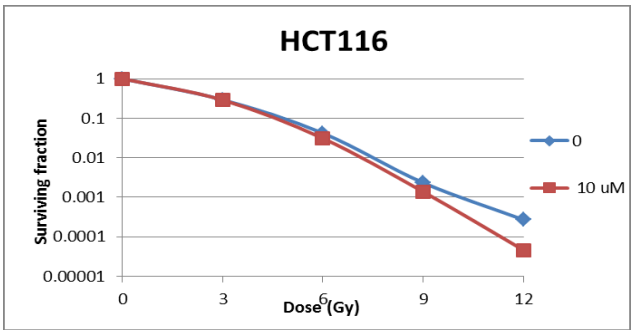
To confirm the lack of radiosensitisation in all 3 colorectal cancer cell lines, clonogenic survival assays were performed as described above. All 3 colorectal cancer cell lines had sufficient plating efficiency for definitive conclusions to be made. Results are shown in Figure 3, confirming that regorafenib does not cause any statistically significant radiosensitisation of colorectal cancer cell lines in this model system.



Drug with radiation



Drug with radiation



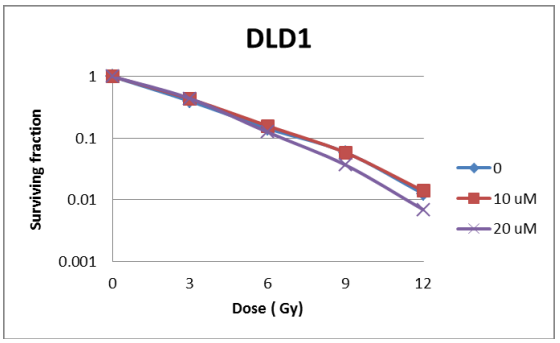


Figure 3

Figure 3. Clonogenic survival assays for 3 colorectal cancer cell lines treated with regorafenib (10 or 20 µM) plus radiotherapy (6 Gy). Slight radiosensitisation of RKO cells was observed with 20 µM regorafenib plus radiation, but no statistically significant radiosensitisation was observed to justify further preclinical testing in vivo. Results shown are mean values of three separate experiments.

Conclusions

We have applied 2 types of laboratory assay, including the gold standard test (clonogenic survival), to confirm that regorafenib is not an intrinsic radiosensitiser of colorectal cancer cells. This model system allows assessment of intrinsic radiosensitisation, but it should be noted that it cannot assess the antiangiogenic effect on radiosensitisation. Such exploration would require in vivo experimentation in an animal model, which is beyond the scope of this study. The rest of the project will test other approved drugs for intrinsic radiosensitisation of colorectal cancer cell lines and hepatoma cell lines and a further report will be issued in October 2013.

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