Protocol Number:	TS-102
Protocol Short Title:	EPOCH
Protocol Name:	A Phase III Clinical Trial **E**valuating TheraSphere® in **P**atients with Metastatic Colorectal Carcinoma **o**f the Liver who have Failed First Line **Ch**emotherapy
US Sponsor:	Frances Harrison BTG International Inc. Five Tower Bridge, Suite 800 300 Barr Harbor Drive West Conshohocken, PA 19428, USA (P) 610 943 3643 (F) 610 943 6018
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Device:	TheraSphere, Yttrium-90 Glass Microspheres
FDA File #:	IDE G100324
Protocol Date Activated:	2011-03-07 (YYYY/MM/DD)
Amendment Date Activated:	Version 2.0, 2012/01/10 Version 3.1, 2013/04/08 Version 4.0, 2013/09/06 Version 5.0, 2014/03/05

	Version 5.1, 2014/05/30 Version 6.1 2016/01/08 Version 7.0 2017/05/10

PROTOCOL APPROVAL AND RELEASE SIGNATURE PAGE

Protocol Title: A Phase III Clinical Trial Evaluating TheraSphere® in Patients with Metastatic Colorectal Carcinoma to the Liver who have Failed First Line Chemotherapy

Protocol #: TS-102

Protocol Approval Date:
Version 1.0 2011-03-07 (YYYY/MM/DD)
Version 2.0 2012-01-10
Version 3.1 2013-04-08
Version 4.0 2013-09-06
Version 5.0 2014-03-05
Version 5.1 2014-05-30
Version 6.1 2016-01-08
Version 7.0 2017-05-10

The above-referenced protocol was reviewed and approved for release by the following:

Co-Principal Investigator

Mary Mulcahy, MD
Global Principal Investigator

Signature

2017/05/11
Date (YYYY/MM/DD)

Co-Principal Investigator

Ricky Sharma, MA MB BChir FRCP FRCR PhD
Global Principal Investigator

Signature

Date (YYYY/MM/DD)

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_____ **Date (YYYY/MM/DD)**

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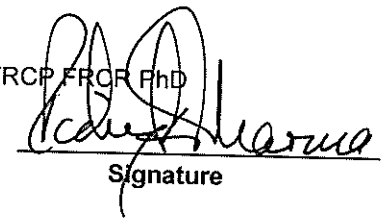
Global Principal Investigator



Signature

15 MAY 2017
Date (YYYY/MM/DD)

US Sponsor

Frances Harrison
SVP, Regulatory Affairs
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Signature

5/10/2017
Date (YYYY/MM/DD)

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2017/May/10th
Date (YYYY/MM/DD)

Nikhil Chauhan, PhD
Director, Biostatistics

Signature

2017/05/10
Date (YYYY/MM/DD)

INVESTIGATOR'S PROTOCOL REVIEW STATEMENT

By my signature, I confirm that my staff and I have carefully read and understand the protocol, A Phase III Clinical Trial Evaluating TheraSphere® in Patients with Metastatic Colorectal Carcinoma of the Liver who have Failed First Line Chemotherapy, and agree to conduct the trial in accordance with the protocol, the appropriate regulations specified in the protocol, and the stipulations of the clinical study agreement.

_____ _____

Investigator Date

_____

Print Investigator Name

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1. PROTOCOL SYNOPSIS

Protocol Number	TS-102
Protocol Short Title	EPOCH
Protocol Title	A Phase III Clinical Trial Evaluating TheraSphere in Patients with Metastatic Colorectal Carcinoma of the Liver who have Failed First Line Chemotherapy
Device	TheraSphere, Yttrium-90 glass microspheres In the European Union, TheraSphere has been CE marked for the treatment of hepatic neoplasia. TheraSphere is currently approved in Canada for treatment of hepatic neoplasia in patients who have appropriately positioned arterial catheters. TheraSphere is currently approved for commercial distribution in the United States under a Humanitarian Device Exemption (HDE) for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment.
Standard-of-Care Chemotherapy	All patients will be treated with standard-of-care second line chemotherapy consisting of either an irinotecan-based regimen, or an oxaliplatin-based regimen. The addition of biological agents approved for use in the second-line setting of mCRC treatment to date (bevacizumab, cetuximab, panitumimab, aflibercept, ramucirumab) is permitted. The biological agents are administered at the investigator discretion, per local practices and according to the approved labels which determine the target patient population and define the full prescribing information.
Type of Protocol	Phase III
Protocol Design	This is an open-label, prospective, multi-center, randomized clinical trial.
Study Objective	The objective of this study is to evaluate the efficacy and safety of TheraSphere in patients with metastatic colorectal cancer of the liver who have progressed with first line chemotherapy.
Primary Endpoints	Progression-Free Survival (PFS) according to RECIST Criteria v.1.1 from time of randomization Hepatic Progression-Free Survival (HPFS), defined as the time from randomization to the date of disease progression in the liver according to RECIST 1.1, or death. The study will be considered to have met its objective if at least one of the primary endpoints is statistically significant.
Secondary Endpoints	• Overall Survival (OS) Time, calculated from randomization to death. • Time to symptomatic progression (TTSP) from the time of randomization to assessment of ECOG performance status >2. Deterioration in performance status is to be confirmed at one subsequent evaluation 8 weeks later. • Objective Response Rate (ORR): per RECIST criteria v 1.1 • Disease Control Rate (DCR): per RECIST criteria v 1.1

	• Quality of Life Assessment: Functional Assessment of Cancer Therapy – colorectal cancer (FACT-c). • Adverse events and reportable serious adverse events as defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events; CTCAE v. 4.0).
Trial Population	Patients with metastatic colorectal carcinoma (mCRC) of the liver who have disease progression with first line chemotherapy either; 1) an oxaliplatin-based regimen, or 2) an irinotecan-based regimen, and who are eligible for second line chemotherapy with the alternate chemotherapy regimen.
Number of Patients	Approximately 420 randomized patients are planned .
Number of Sites	Up to 100 sites in the United States, Canada, Europe and Asia
Treatment Groups	For all patients, all chemotherapy, including biological agents (i.e. VEGF inhibitors or others), must be stopped at least 14 days prior to starting 2nd line chemotherapy and 28 days prior to the administration of TheraSphere. Patients randomized to the Treatment Group must initiate 2nd line chemotherapy, within a maximum of 21 days of randomization. TheraSphere is to be administered in place of the second chemotherapy cycle. Biological therapy can be added for patients randomized to the Treatment Group, 2 weeks after the TheraSphere administration (i.e. with the next cycle of the standard-of –care chemotherapy). ***(Note:** For the purpose of this study, one cycle is defined as a chemotherapy infusion.)* Patients randomized to the Control Group will initiate 2nd line chemotherapy within 21 days of randomization. Biological agents can start with the first cycle of second line chemotherapy for patients randomized to the control group.
Trial Duration	Approximately 60 months of accrual and 1 year additional follow-up are planned. ***Note:*** the sample size calculation, in terms of the number of patients, is based on an accrual period of 36 months and 12 months of additional follow-up. However, since the timing of the interim and final analyses is based on the number of PFS events, the increase in the forecasted accrual period to 60 months, does not increase the number of patients required, or affect the statistical power of the study.

Eligibility Criteria	Patients must meet all eligibility criteria: 1. Must be male or female, 18 years of age or older, and of any ethnic or racial group 2. If primary tumor has not been resected, it must be clinically stable 3. Must have colorectal cancer with unresectable metastatic disease to the liver (unresectable unilobar or bilobar disease) who have disease progression in the liver with oxaliplatin or irinotecan based first-line chemotherapy; 4. Must be eligible to receive second-line standard-of-care chemotherapy with either: 1) an oxaliplatin-based chemotherapy regimen, or 2) an irinotecan-based chemotherapy regimen 5. Must have baseline efficacy images with measurable target tumors in the liver according to RECIST 1.1 using standard imaging techniques taken within 28 days prior to randomization. Images must be taken after, or at the time of completion of first line chemotherapy 6. Tumor replacement $\leq$50% of total liver volume 7. Current Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-1 through screening to first treatment on study 8. Will have completed the first line chemotherapy regimen at least 14 days prior to the initiation of 2nd line chemotherapy under the protocol 9. Patient is willing to participate in the study and has signed the study informed consent 10. Serum creatinine $\leq$2.0 mg/dL 11. Serum bilirubin up to 1.2 x upper limit of normal 12. Albumin $\geq$3.0 g/dL 13. Must not have a history of hepatic encephalopathy 14. Must not have any contraindications to angiography and selective visceral catheterization such as bleeding diathesis or coagulopathy that is not correctable by usual therapy of hemostatic agents (e.g. closure device) 15. No history of severe peripheral allergy or intolerance to contrast agents, narcotics, sedatives or atropine that cannot be managed medically 16. Must have neutrophil count >1200/mm^3 (1.2x10^9/L) 17. No presentation of pulmonary insufficiency or clinically evident chronic obstructive pulmonary disease 18. No cirrhosis or portal hypertension 19. Must not have received any prior external beam radiation treatment to the liver 20. Must not have received any prior intra-arterial liver-directed therapy, including TACE or Y-90 microsphere therapy

	21. Must not have any planned liver-directed therapy or radiation therapy 22. Must not have planned treatment with biological agents within 28 days prior to receiving TheraSphere 23. Must not have undergone any intervention for, or compromise of, the Ampulla of Vater 24. Must not have any clinically evident ascites (trace ascites on imaging is acceptable) 25. Must not have any toxicities due to prior cancer therapy that have not resolved before the initiation of study treatment, if the Investigator determines that the continuing complication will compromise the safe treatment of the patient 26. Must not have any significant life-threatening extra-hepatic disease, including patients who are on dialysis, have unresolved diarrhea, have serious unresolved infections including patients who are known to be HIV positive or have acute HBV or HCV 27. Must not have any confirmed extra-hepatic metastases. Limited, indeterminate extra-hepatic lesions in the lung and/or lymph nodes are permitted (up to 5 lesions in the lung, with each individual lesion <1 cm; any number of lymph nodes with each individual node <1.5 cm) 28. Must not have any contraindications to the planned second line standard-of-care chemotherapy regimen 29. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to randomization, must not be breastfeeding, and must agree to use contraceptive for duration of study. 30. Must not have participated in a clinical trial with an investigational therapy within 30 days prior to randomization 31. Must not have any co-morbid disease or condition that would place the patient at undue risk and preclude safe use of TheraSphere treatment, in the Investigator's judgment
Imaging Requirements	The primary efficacy endpoints progression free survival (PFS) and hepatic progression-free survival (HPFS), and secondary efficacy endpoint of disease control rate (DCR) will be based on imaging evidence of disease progression. Patients will have baseline images for disease assessment taken within 28 days prior to randomization and every 8 weeks from randomization (+/- 1 week) during the study to evaluate disease progression. A confirmatory image at the next subsequent visit following progression is required and may be scheduled outside of the 8-week window. In addition to the confirmatory scan, all images performed according to the local standard practices should be collected until hepatic progression is confirmed. These images do not have to conform to an 8-week schedule. All disease assessment images including the baseline images must be assessable according to RECIST 1.1. Baseline images conducted in the course of standard-of-care clinical management may be used if the images conform to RECIST 1.1 and are taken after, or at the time of completion of first line chemotherapy. All imaging studies from baseline to progression

	will require a duplicate set of images in DICOM format to be submitted to the sponsor for blinded independent central image review analysis. • CT scans for the assessment of liver metastases must include a portal venous phase • Spiral CT/MRI abdomen/pelvis –performed with cuts of 5 mm or less in slice thickness contiguously in the axial plane to assess hepatic and extra-hepatic lesions according to the RECIST criteria v1.1. • Spiral CT/MRI Chest –performed with cuts of 5 mm or less in slice thickness contiguously in the axial plane to assess extra-hepatic lesions according to the RECIST criteria v 1.1.
Other Variables	Labs – Blood will need to be drawn for the following labs to test liver function and pregnancy as part of standard-of-care clinical management with results documented in the electronic case report form. Progression of disease will be monitored through tumor markers: • Hematology (WBC with differential, Hgb, Hct, Platelet) • Coagulation (PT, PTT, INR) • Chemistry Panel, Liver function tests • Serum Pregnancy test (as appropriate) • CRC Tumor Marker: Serum CEA ECOG Performance Status
Statistical Plan and Sample Size Calculation	This study is an adaptive trial using a group sequential design with PFS and HPFS as the primary endpoints. The study could be stopped early for efficacy at an interim analysis based on superiority in PFS but not HPFS. The study is designed to detect a 2.5 month increase in median PFS time, from 6 months in the control arm to 8.5 months in the TheraSphere arm (ie, hazard ratio [HR] = 0.71), and a 3.5 month increase in median HPFS time, from 6.5 months in the control arm to 10 months in the TheraSphere arm (ie, HR = 0.65), using log rank tests. The analysis of PFS will be based on a group sequential design with 2 interim analyses and rho family error spending function stopping boundary with rho=1.5. It is estimated that approximately 420 patients will need to be recruited over 36 months, with a 1 year additional follow-up period, allowing for 10% of patients lost to follow-up and for whom a date of progression or death is not recorded. Although the forecasted accrual period has been increased to 60 months, this does not increase the number of patients required, or affect the statistical power of the study since both the power and the timing of the interim and final analyses are based on the number of PFS events rather than the number of patients. The Hochberg procedure (Hochberg, 1988) will be used to control Type I error for the two primary endpoints at the final analysis. A simulation study, assuming that PFS and HPFS have a correlation between 0.3 and 0.8, showed that the power to detect the target difference in either median PFS (ie, HR=0.71) or median HPFS (ie, HR=0.65) is >90%, and the power

	to detect the target difference in PFS or HPFS alone is >80%. The simulation study also demonstrated control of Type I error. Analysis of primary endpoints: PFS and HPFS will be compared between treatment arms using log-rank tests at an overall one-sided alpha level of 0.025, to test the null hypothesis that the hazard rates for the treatment and control arms are equal versus the alternative hypothesis that the hazard rate for the TheraSphere arm is less than the hazard rate for the control arm, ie, $H_0: \lambda_T = \lambda_C$ versus $H_1: \lambda_T < \lambda_C$, where λ_T and λ_C represent the PFS or HPFS hazard rates for the TheraSphere and control arms respectively. The hazard ratio and two-sided 95% confidence limits for the treatment effect will be computed. Kaplan-Meier curves will also be produced. Log rank tests converted to z-scores will be used to compare the primary endpoints between the treatment arms. Interim Analyses of primary endpoint of PFS: The first interim analysis is planned at 172 PFS events. PFS will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.372 based on the rho family error spending function corresponding to a one-sided p-value ≤0.0088 allowing the study to be stopped early for efficacy, in which case HPFS will be tested at the same boundary as PFS using a log rank test converted to a z-score. A second interim analysis is planned at 241 PFS events, where PFS will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.330 based on the rho family error spending function corresponding to a one-sided p-value ≤0.0099 allowing the study to be stopped early for efficacy. If the study is stopped early for PFS at the second interim analysis, HPFS will be tested using the boundary derived based on an incremental alpha of 0.0057. This boundary will account for the correlation between the z-score for HPFS at the first interim analysis and the z-score for HPFS at the second interim analysis, which is determined by the observed number of HPFS events at the first interim analysis and the cumulative number of HPFS events observed at the second interim analysis. At each of the interim analyses, if the conditional power for both PFS and HPFS is less than 15% the study could be stopped early for futility.

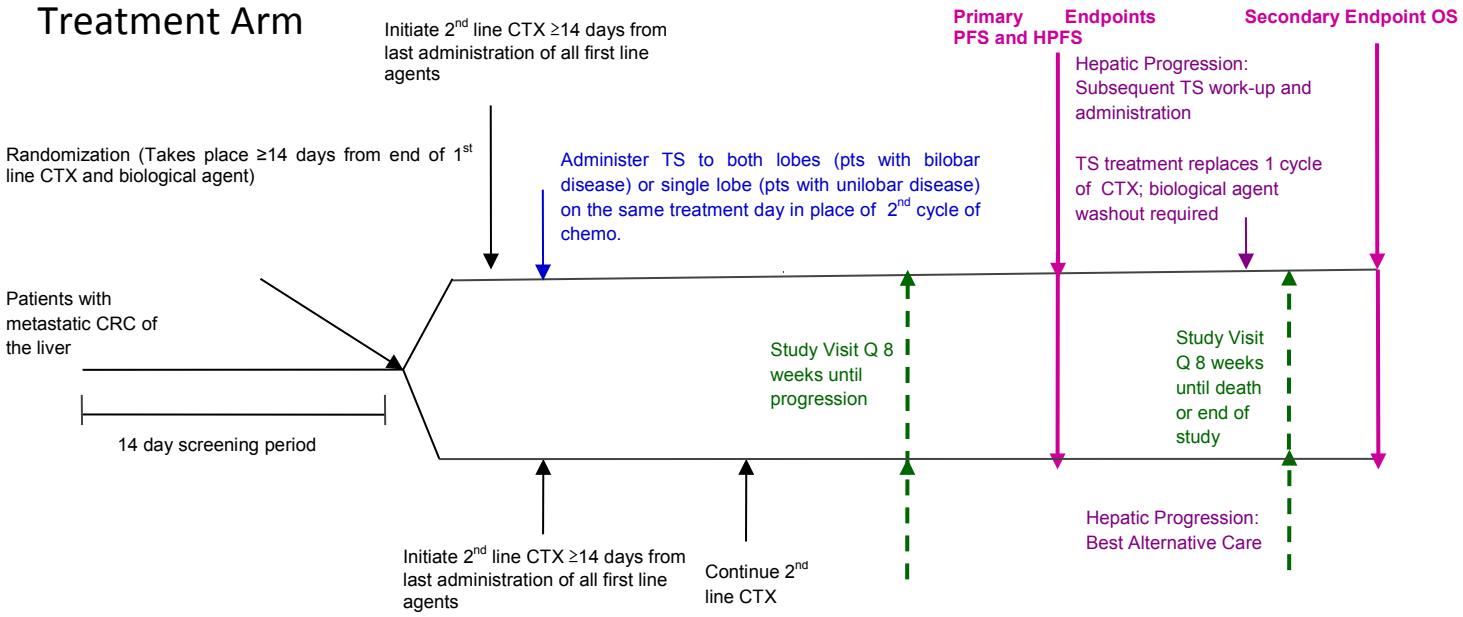
	Final Analysis of primary endpoints of PFS and HPFS: The final analysis is planned at 344 PFS events. The Hochberg procedure (Hochberg, 1988) will be used to control Type I error for the two primary endpoints. Whichever of PFS or HPFS that has the larger p-value, will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.312 with a corresponding one-sided p-value ≤0.0104 required to declare a statistically significant improvement in hazard rate for this endpoint. To ensure that Type I error is controlled for both primary endpoints, this boundary is based on the incremental alpha of 0.0104 instead of the p-value scale boundary of 0.0168, using the rho family error spending function with rho=1.5. According to the Hochberg procedure, if the primary endpoint with the larger p-value is statistically significant then the other primary endpoint is also statistically significant. However, if the primary endpoint with the larger p-value is not statistically significant then the other primary endpoint will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.562 based on the rho family error spending function, with a corresponding one-sided p-value ≤0.0104/2 = 0.0052 required to declare a statistically significant improvement in hazard rate for this endpoint. Analysis of secondary efficacy endpoints: Comparison between treatment groups for all secondary endpoints will be conducted at the final analysis at α=0.025 (one-sided), only if both of the primary endpoints are statistically significant, with study-wise Type I error controlled using a sequential hierarchical approach, according to the following ordering of secondary endpoints: OS→ TTSP→ORR→DCR→TTDQoL. Time to event endpoints (ie, OS, TTSP, TTDQoL) will be compared between treatment arms using a log-rank test. Disease control rates and ORR will be compared between treatment arms using the continuity adjusted Newcombe-Wilson test. The FACT-c score will be compared between treatment arms using a mixed linear model with baseline score and the relative time from baseline as covariates. Safety Analysis: All patients who received study treatments at least once will be included in the safety analysis. All adverse events will be reported according to the NCI grades and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment emergent adverse events (events which were not present at baseline or worsened in severity following the start of treatment) will be summarized according to MedDRA primary system-organ class (SOC) and preferred term (PT). Laboratory values will be summarized by treatment group over time and overall. A feasibility safety assessment will be conducted after the first 20 patients in

	the Treatment group have received both TS and chemotherapy. Poolability: As a sensitivity analysis, to address the poolability of data across regions, study sites and gender, a Cox regression analysis of the primary efficacy endpoints, PFS and HPFS, will be conducted including additional factors of region, study site and gender, and to determine the impact of these factors on PFS and HPFS. If the poolability of PFS and HPFS results is in direct question as a result of this sensitivity analysis, the primary endpoints (PFS and HPFS) will also be analyzed separately by region, site or gender. In addition, the primary endpoints (PFS and HPFS) will be analyzed separately by US and non-US region.
Screening/Baseline Test Period	Patients with colorectal cancer liver metastases who have progressed with a first line chemotherapy regimen (either oxaliplatin-based or irinotecan-based regimen), and are eligible for a standard-of-care second line regimen may be screened for inclusion into this study. The baseline tests should be performed within 14 days prior to randomization. Results of tests conducted in the course of standard-of-care clinical management taken within the baseline period may be used. Evaluations include: • Baseline images for efficacy assessment will be taken within 28 days prior to randomization. The baseline disease assessment images must also have been taken after, or at the time of completion of first line chemotherapy. Baseline disease assessment images must have measurable target tumors in the liver and be assessable according to RECIST 1.1. Informed Consent (before any study required tests are performed), • Physical examination, • Medical history, • ECOG assessment of performance status, • Quality of Life Questionnaire (FACT-C), • Laboratory blood tests, including serum CEA • Baseline chest/abdomen/pelvis images to assess liver tumor presentation and assess tumor burden
Randomization	Upon meeting eligibility for trial participation in accordance with the Eligibility criteria, patients will be randomized 1:1 between the Treatment and Control groups. Prior to randomization, the investigator will decide which chemotherapy regimen, including drugs, doses and biological agents, is to be given as second-line treatment. This planned treatment is to be administered regardless of the arm to which the patient is randomized (Control or Treatment). The only exception being that the addition of biological agents for those randomized to the Treatment Group may only begin with the chemotherapy cycle following the treatment with TheraSphere. In order to ensure that the treatment groups are balanced, patients will be stratified at randomization according to; the presence of unilobar or bilobar disease; oxaliplatin or irinotecan based first-line chemotherapy; and KRAS

	status. Patients randomized to the Control group or the Treatment group who are unable to receive their planned study treatment will continue to be followed under their assigned study group for the purpose of the intent-to-treat analysis. The date of screening is the date all screening procedures are completed.
Initiation of Study Treatment and Early Treatment Cycles	The chemotherapy regimen, including dose and type of biological agent, must be decided and documented prior to randomization. Patients randomized to the Control group must begin standard-of-care second-line chemotherapy within 21 days of randomization Biological agents can start along with the first cycle of second-line chemotherapy for patients randomized to the Control group. Patients randomized to the Treatment group must begin standard-of-care second-line chemotherapy within 21 days of randomization. Biological agents can be added for patients randomized to the Treatment Group, a minimum of 2 weeks (+/- 2 days) after the TheraSphere administration (i.e. with the next cycle of the standard-of–care chemotherapy).
TheraSphere Treatment Procedure	For patients randomized to the Treatment group, hepatic angiography will be performed to assess hepatic vascular anatomy and tumor hypervascularity, followed by a ^{99m}Tc-MAA scan to rule-out gastrointestinal flow or unacceptable lung shunting. Embolization may be performed, if necessary, to close off gastrointestinal flow. These evaluations should be scheduled as soon as possible after randomization, but TheraSphere treatment can only take place at least 28 days after the discontinuation of biological agents. Patients will not be eligible to receive TheraSphere infusion if the potential radiation dose to the lungs exceeds 30 Gy for a single treatment or cumulative 50 Gy or embolization cannot be performed to effectively block GI blood flow from the hepatic arterial system. In this case, patients should continue with their planned standard-of-care second line chemotherapy treatment. In patients with bilobar disease, TheraSphere treatment should be administered to both lobes on the same day. In patients with unilobar disease, TheraSphere should be administered to the lobe where disease is present. The number of infusions required will be determined by the Investigator, based on the hepatic vascular anatomy. TheraSphere treatment can be performed in the inpatient or outpatient setting. Patients will receive a target dose of 120 ± 10% Gy of TheraSphere. An interval of two weeks after the previous cycle of chemotherapy and two weeks before the next cycle is required. For patients randomized to the Treatment Group, subsequent TheraSphere administration to newly observed liver lesions following disease progression is permitted in patients who are amenable to further TheraSphere treatment.
Second line Chemotherapy	The chemotherapy regimen, including dose and type of biological agent, must be decided and documented prior to randomization. All randomized patients will follow their planned second-line treatment regimen until disease progression, death or intolerable toxicity in accordance with standard medical practice, including any adjustments to the planned

	treatment doses and schedule for reasons of toxicity.
Trial Visits and Follow-up	• Screening and Randomization • Every 2 Weeks following randomization: Patients return to the clinic for chemotherapy administration and safety assessment. Visit activities include standard-of-care clinical management laboratory evaluations, performance status, recording and assessment of adverse events, and administration of chemotherapy. • Every 8 Weeks following randomization until hepatic progression: imaging for disease assessment (see above) • Every 8 Weeks following progression until death or end of study: clinic visits for safety assessment
Central Image Review	CT/MRI images will be reviewed centrally prior to the interim and final analyses. The central image reader will be qualified by training and experience. The analysis for the interim and final reports will be based upon the readings of the central reviewer. In cases of dispute between the site and the central reviewer, the central reviewer will prevail.
Independent Data Monitoring Committee	This study will have oversight by an Independent Data Monitoring Committee (IDMC) who will meet as determined to review the enrollment, protocol deviations, and safety events. They will evaluate the data at interim analyses for consideration of stopping the study for overwhelming efficacy or futility. The IDMC will evaluate the final study report.

2. TRIAL SCHEMA



Legend

CTX: chemotherapy

CRC: colorectal cancer

HPFS: Hepatic Progression Free Survival

OS: Overall Survival

PFS: Progression Free Survival

Pts: patients

TS: TheraSphere

*Note –one cycle of chemotherapy is given prior to treatment with TheraSphere.

3. SCHEDULE OF EVENTS

Evaluation/Test **Timing of Visit(s)**	**Screen** **Day -14 to 0**	**Rand-omize** **Study Day 0**	**Chemo-therapy** **Q 2**	**1st TS work up & Admin-istration** **(replaces second cycle)**	**Study Visits to Progress-ion** **Q 8 weeks from randomization (+/- 1 week)**	**Additional TS work up & Admin-istration** **Post hepatic progression, TS Replaces a cycle of chemo**	**Study Visits Until Death or End of Study** **Q 8 weeks (+/- 1 week)**
Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Exam (PE)	X						
ECOG Performance Status	X		X[7]	X	X	X	X[7]
Medication & Prior Treatment History	X						
Review Eligibility Criteria	X						
Hematology: WBC with Diff Hgb, Hct, platelet	X		X		X	X	
Coagulation: PT, PTT, INR	X		X[1]			X	
Chemistry panel, liver function tests	X		X		X	X	
Serum Pregnancy[2]	X			X		X	
Tumor markers for CRC (CEA)	X				X		
Liver Volume/Mass Calculation				X		X	
Estimation of Tumor Burden[3]	X						

[1] Only required at chemo visits as clinically indicated (i.e. if patient is being followed for coagulopathy)
[2] Required for female patients of childbearing potential
[3] Required for Screening Purposes, may be visual or volumetric assessment
[4] TS patients only
[5] All randomized patients: all patients must receive a study treatment (Chemo) within 21 days of randomization

Evaluation/Test **Timing of Visit(s)**	**Screen** **Day -14 to 0**	**Rand-omize** **Study Day 0**	**Chemo-therapy** **Q 2**	**1st TS work up & Admin-istration** **(replaces second cycle)**	**Study Visits to Progress-ion** **Q 8 weeks from randomization (+/- 1 week)**	**Additional TS work up & Admin-istration** **Post hepatic progression, TS Replaces a cycle of chemo**	**Study Visits Until Death or End of Study** **Q 8 weeks (+/- 1 week)**
Documentation of Type and dose of chemo and biologics	X						
Randomize Patient		X					
Hepatic Angiogram, ^{99m}Tc-MAA scan, TS Dose Calculation				X		X	
Order TS[4]				X		X	
Administer TS [4]				X		X	
Administer 2nd line Chemotherapy[2]			X				
Record/Administer any Chemotherapy following 2nd line[5]							X
QOL questionnaire	X				X		X[7]
Spiral CT /MRI of abdomen/pelvis/chest [8]	X				X	X	
Assess/Report Adverse Events			X	X	X	X	X
Review/Record Concurrent Medication	X		X	X	X	X	X
Final Endpoint Efficacy/Safety documentation & exit patient							X

[6] Additional approved chemotherapy for CRC may be administered only after progression of 2nd line chemotherapy
[7] Can be done remotely if patient is not coming in for clinic visit
[8] all attempts should be made to image every 8 weeks until hepatic progression, plus confirmatory scan (see main text)

4. LIST OF ABBREVIATIONS

AE - Adverse Event

ALT – Alanine Transaminase

AST – Aspartate Transaminase

BUN – Blood Urea Nitrogen

CBC – Complete Blood Count

CEA – Carcinoembryonic Antigen – CRC tumor marker

CRC – Colorectal Cancer

Cr - Chromium

CT – Computed Tomography

CTCAE – Common Toxicity Criteria for Adverse Events

DCR – Disease Control Rate

DSMB – Data Safety Monitoring Board

ECOG – Eastern Cooperative Oncology Group

eCRF – Electronic Case Report Form

EGFR – Epidermal Growth Factor Receptor

FACT-c – Functional Assessment of Cancer Therapy - colorectal

FDA – Food and Drug Administration (United States)

FOLFIRI – irinotecan-based chemotherapy

FOLFOX – oxaliplatin-based chemotherapy

GBq - GigaBecquerel

GI – Gastrointestinal

Gy – Gray, a measure of irradiation dose

HCC – Hepatocellular Carcinoma

HDE – Humanitarian Device Exemption

HPFS – Hepatic Progression Free Survival

ICF – Informed Consent Form

IDMC – Independent Data Monitoring Committee

INR – International Normalized Ratio for prothrombin time

IRB – Institutional Review Board

ITT – Intent–to-Treat

KRAS **- V-**Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

LFT – Liver Function Tests

mCRC – metastatic colorectal carcinoma

MR, MRI – Magnetic Resonance, Magnetic Resonance Image

NCCN – National Comprehensive Cancer Network (United States)

NCI – National Cancer Institute

ORR – Objective Response Rate

OS – Overall Survival

QoL – Quality of Life

PE – Physical Exam

PFS – Progression Free Survival

PP-Per Protocol

PT - Prothrombin Time

PTT – Partial Thromboplastin Time

RECIST – Response Evaluation Criteria in Solid Tumor

SAE – Serious Adverse Event

SOC – Standard of Care

^{99m}Tc-MAA – Technetium-99m Magroaggregated albumin

TS - TheraSphere

TTP – Time-to-Progression

TTSP- Time to symptomatic progression

UADE – Unanticipated Adverse Device Effect

UPFS – Untreatable Progression-Free Survival

VEGF inhibitor – Vascular Endothelial Growth Factor inhibitor

WBC – White Blood Cells

Y-90 (Y-88, Y-91) – Ytrium-90 and isotopes

5. BACKGROUND AND RATIONALE

5.1 GENERAL DEVICE DESCRIPTION

TheraSphere® (TS) consists of insoluble glass microspheres in which yttrium-90 (Y-90) is an integral component of the glass. The sphere diameter ranges from 20 to 30 µm with 22,000 to 73,000 microspheres per milligram. TheraSphere is available in dose sizes ranging from 3 to 20 GBq (typically 3 GBq, 5 GBq, 7 GBq, 10 GBq, 15 GBq and 20 GBq) each supplied in 0.6 mL of sterile, pyrogen-free water contained in a 1.0 mL vial secured within a clear acrylic vial shield. A pre-assembled single-use TheraSphere Administration Set is provided for each dose. Each user site is provided with a re-useable TheraSphere Administration Accessory Kit that provides both radiation protection for the user and physical support of the dose vial and Administration Set during administration of the product.

Yttrium-90 is a pure beta emitter which decays to stable zirconium-90 with a physical half-life of 64.1 hours. The average energy of the beta emissions from yttrium-90 is 0.9367 MeV with mean tissue penetration of approximately 2.5 mm.

TheraSphere is administered through the hepatic artery which supplies blood to tumor tissue (the portal vein supplies blood to the normal hepatic tissue). The microspheres are trapped in the vasculature of the tumor due to arteriolar capillary blockage where they exert a local radiotherapeutic effect. In clinical use, the glass microspheres remain permanently trapped in the vasculature where the isotope decays to infinity leaving background radiation with no therapeutic value.

5.2 GLOBAL REGULATORY STATUS OF THERASPHERE

TheraSphere received a Humanitarian Device Exemption (HDE) from the United States Food and Drug Administration (FDA) in 1999 (HDE H980006) and is currently approved for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment. The current package insert approved by the United States Food and Drug Administration (FDA) is provided in Appendix 1a.

TheraSphere is approved for use in Europe for the treatment of hepatic neoplasia. TheraSphere is approved in Canada for the treatment of hepatic neoplasia in patients who have appropriately positioned arterial catheters. In addition, TheraSphere is available in South Africa, Turkey, Saudi Arabia, Singapore, Hong Kong and South Korea for the treatment of hepatic neoplasia. The current package inserts from Canada and Europe are provided in Appendix 1b and 1c respectively.

5.3 US CLINICAL EXPERIENCE WITH THERASPHERE IN PATIENTS WITH METASTATIC LIVER CANCER

Since 2004, more than 500 patients in the United States with metastatic liver cancer have been treated with TheraSphere under a named-patient compassionate use process. This program was terminated in late 2009. As of October 2009, follow-up information for more than 400 patients in

this program has been reported to the FDA with data for a subset of more than 190 patients published in the literature.

In addition, an open-label, single group, Phase II clinical trial in patients with metastatic liver cancer was initiated in 2007. The primary outcome measure of this Phase II study was safety. Enrollment in this study was completed at 151 patients. The last patient exited this study on March 30th 2011 and the data was submitted to the FDA as part of a Clinical Study Report in September 2011. The safety results from this Phase II trial are consistent with those reported under the named-patient compassionate use program and include fatigue, pain, nausea/vomiting and transient laboratory abnormalities.

Early reports of serious adverse events possibly associated with the use of TheraSphere included death, hepatorenal failure, liver abscess, hepatic encephalopathy, hepatic decompensation, radiation hepatitis, radiation pneumonitis, duodenal ulcer, gastrointestinal bleeding and cholecystitis. As clinical experience with TheraSphere increased, the pre-treatment risk factors associated with these early serious adverse events were identified, leading to improved patient selection criteria, and thereby lowering the risk of these events occurring. Patients in whom TheraSphere should be used with caution include those with infiltrative tumor type, bulk disease (tumor volume >70% or nodules too numerous to count), AST (aspartate transaminase) or ALT (alanine transaminase) > five times the upper limit of normal, bilirubin > 2 mg/dL, tumor volume >50% in the presence of an albumin < 3 g/dL and those in whom extra-hepatic shunting to the lungs or gastrointestinal tract cannot be managed through standard angiographic techniques.

For those patients without the pre-treatment high risk factors noted above, TheraSphere is very well tolerated, with treatment administered in an outpatient setting. Hospitalization for treatment effects is rarely required. The most commonly reported adverse events associated with TheraSphere are fatigue, abdominal pain, nausea/vomiting and transient laboratory values including elevated bilirubin, AST, ALT, alkaline phosphatase, decreased platelets and lymphocyte depression with no clinical sequelae.

5.4 RATIONALE FOR TREATMENT OF LIVER METASTASES SECONDARY TO COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer diagnosed among both men and women in the US. The American Cancer Society[1] estimates that approximately 148,810 new cases of colorectal cancer and 49,960 deaths were expected in 2008. Approximately 72% of new diagnoses are colon cancer and 28% are rectal cancer.

Because the liver is the most frequent site of metastases, an estimated 60% of patients who are diagnosed with CRC eventually will experience liver disease as a predominant site[2]. Consequently, much of the morbidity and mortality in patients with CRC[3] is due to unresectable liver metastases. A median overall survival of 44 months and a 5-year survival rate of 35%[4] are associated with surgical resection of liver-confined disease for patients with no evidence of disseminated disease with a resection strategy encompassing all liver disease with adequate remnant liver for recovery and medical fitness for laparotomy. However, patients who have liver metastases amenable to resection are less than 20% of the population with metastatic liver disease[5], a rate that may improve with current chemotherapy. For the majority of patients without resectable disease, the

median overall survival is 22 months and rarely is associated with survival beyond 5 years[6]. Targeted non-surgical approaches for liver-confined CRC metastases may offer survival advantages beyond that of systemic therapy alone.

TheraSphere was evaluated in a cohort of seventy-two patients[7] with unresectable hepatic colorectal metastases who were treated at a targeted absorbed dose of 120 Gy with a median delivered dose of 118 Gy. The safety and toxicity of TheraSphere was assessed using version 3 of the National Cancer Institute Common Terminology Criteria. Response was assessed radio-graphically and survival estimated using the Kaplan-Meier method from the diagnosis of hepatic metastases and first treatment. Treatment-related toxicities included fatigue (61%), nausea (21%), and abdominal pain (25%) with Grade 3 and 4 bilirubin toxicities observed in 9 of 72 patients (12.6%). The tumor response rate was 40.3%. The median time to hepatic progression was 15.4 months, and the median response duration was 15 months. Overall survival from the first TheraSphere treatment was 14.5 months. Based on sub-stratification analyses, tumor replacement (≤25% vs >25%) was associated with significantly greater median survival (18.7 months vs 5.2 months). The presence of extrahepatic disease was associated negatively with overall survival (7.9 months vs 21 months). Overall survival from the date of initial hepatic metastases was 34.6 months. A subset analysis of patients who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 demonstrated a median survival of 42.8 months and 23.5 months from the time of hepatic metastases and TheraSphere treatment, respectively. The data from this study also suggests that patients who have been exposed to fewer than three cytotoxic agents may have a better outcome than patients who have received all chemotherapy options prior to treatment with TheraSphere.

Based on the subset analyses of this study, it appears patients with good performance status, no extrahepatic metastases, liver disease limited to ≤25% of liver volume, who have not received all available lines of chemotherapy may benefit most from treatment with TheraSphere. We therefore propose to evaluate the outcome of these patients when TheraSphere is added to second line standard-of-care chemotherapy.

The most recent National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology8(NCCN - Colon Cancer V.3.2015 - COL-C – Appendix 3) note that current chemotherapeutic options for the treatment of colorectal cancer, may include but are not limited to, fluoropyrimidines, irinotecan, oxaliplatin, tyrosine kinase inhibitors, as well as vascular endothelial growth factor- and epidermal growth factor-targeting agents. Section COL-7 of these guidelines recommends the various combinations of these agents that should be used in the first or second line treatment of colorectal cancer. Typically, patients with metastatic colorectal cancer are treated with either an Oxaliplatin or Irinotecan based regimen as first line chemotherapy, with or without the addition of bevacizumab, cetuximab or panitumumab. On progression, patients are treated with the regimen they did not receive during first line chemotherapy. Epidermal growth factor receptor (EGFR) inhibitors may be added in patients with wildtype KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog).

The result of a recent Phase III clinical trial demonstrated that continuing treatment with bevacizumab into second line chemotherapy results in improvements in both PFS and overall survival, as compared to second line chemotherapy alone, if the patient progressed while receiving a bevacizumab containing regimen during first line chemotherapy. [9]

A radioembolization device similar to TheraSphere but composed of resin microspheres has also been evaluated in the treatment of metastatic colorectal cancer. Jakobs[10] et al confirmed the mild to moderate toxicity profile of Y-90 microsphere radioembolization when they reported no severe toxicities, except for one grade 4 treatment-associated cholecystitis and two grade 2 gastric ulcers, using resin-microsphere radioembolization administered as single-session, whole liver treatment in 41 patients with metastatic colorectal cancer refractory to chemotherapy. In dose escalation studies reporting use of the resin microspheres in combination with oxaliplatin[11] based chemotherapy and in combination with irinotecan[12] based chemotherapy, the authors concluded respectively that the maximum-tolerated dose of oxaliplatin was 60 mg/m^2 during the first three cycles of chemotherapy and a maximum-tolerated dose of irinotecan was not reached. In both trials, radioembolization treatment was administered within a cycle of chemotherapy with the majority of patients experiencing mild to moderate transient toxicities.

In this clinical trial, TheraSphere will be administered in place of the second cycle of chemotherapy, ensuring a 2 week period between the radioembolization and chemotherapy.

In this clinical trial, patients with metastatic colorectal cancer and liver only metastases in whom second line chemotherapy treatment is planned using either an oxaliplatin-based or irinotecan-based chemotherapy regimen, will be randomized (1:1) to either the Treatment Group, where TheraSphere will be administered in place of the second cycle of the planned standard-of care-second line chemotherapy, or the Control Group, where patients will be treated with only their planned standard-of-care second line chemotherapy. Patients in both groups must receive a study treatment, either chemotherapy or TheraSphere, within 21 days of randomization.

One of the primary endpoints for this clinical trial is progression free survival (PFS). The outcome assumptions in the Control group are from the Phase III study[13] that investigated second-line FOLFIRI (5-fluorouracil, leucovorin and irinotecan) with or without panitumumab in 1,186 metastatic colorectal cancer patients.

This study met its primary endpoint, with the addition of panitumumab to FOLFIRI showing a statistically significant increased progression-free survival in wild-type KRAS patients of 5.9 months versus 3.9 months for FOLFIRI alone (p=0.004). Panitumumab also resulted in slightly longer overall survival in wild-type KRAS patients with 14.5 months in comparison with 12.5 months for chemotherapy alone (p=0.115), although this was not statistically significant. Overall response rate was higher in the panitumumab arm at 35% compared with 10% in the chemotherapy alone arm. In contrast, between the two treatment arms for mutant KRAS, there was only a negligible difference in progression-free survival (5.0 months for panitumumab versus 4.9 months for chemotherapy alone), overall survival (11.8 months for panitumumab versus 11.0 months for chemotherapy alone). There is a wide variation in the outcomes[14,15] reported with second line chemotherapy in metastatic colorectal cancer, and outcomes in patients with liver only metastases have not been reported.

We have also taken into consideration the recent Phase III trial data by Arnold et al, demonstrating a significant improvement in PFS and overall survival when bevacizumab treatment is continued into second line chemotherapy. In the Arnold study, the median PFS was 5.7 months in patients who progressed on a bevacizumab containing regimen in first line chemotherapy and continued with bevacizumab in combination with their second line chemotherapy regimen as compared to a

median PFS of 4.1 months in patients who continued into second line chemotherapy without bevacizumab.[11]

For our proposed trial, we assume a median PFS of 6 months in the control group, and 8.5 in the treatment group (hazard ratio [HR]=0.71). We also assume a median hepatic PFS (HPFS) of 6.5 months in the control group and 10 months in the treatment group (HR=0.65). The assumption of a median HPFS of 10 months in the treatment group is based on a median HPFS of 9.2 months in a study of 23 patients who received second line yttrium-90 resin microspheres[16].

6. STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and safety of TheraSphere in the treatment of patients with metastatic colorectal cancer of the liver.

7. STUDY DESIGN

This is an open-label, prospective, multi-center, randomized, clinical trial.

Patients with metastatic colorectal carcinoma of the liver, who have disease progression with first line chemotherapy, and in whom the administration of standard-of-care second line chemotherapy with either an oxaliplatin-based regimen, or an irinotecan-based regimen is planned, are eligible to participate. Most patients receive an oxaliplatin-based regimen during first line chemotherapy, therefore it is expected most patients will be receiving an irinotecan-based regimen as their standard-of-care second line regimen while they participate in this trial. However some patients are expected to receive an oxaliplatin-based regimen as their second-line regimen.

Prior to randomization the investigator will decide which chemotherapy regimen, including drugs, doses and type of biological agent is to be given as part of the second line treatment. This planned treatment is to be administered regardless of the treatment arm to which the patient is randomized (control or treatment). The only exception being that the addition of biological therapy for those randomized to the Treatment Group may only begin at the chemotherapy cycle following the treatment with TheraSphere.

Eligible patients will be randomized (1:1) to either the Control Group or the Treatment Group, defined as follows:

Treatment Group: Patients randomized to the Treatment Group will be treated with TheraSphere administered in place of the second cycle of their standard-of-care second line chemotherapy regimen. Subsequent chemotherapy must not begin until a minimum of two weeks (+/- 2 days) after the TheraSphere has been administered. Treatment with first cycle of chemotherapy must begin within 21 days of randomization.

Control Group: Patients randomized to the Control Group will receive only their planned standard-of-care second line chemotherapy regimen. Treatment with chemotherapy must begin within 21 days of randomization.

The addition of approved biological agents (bevacizumab, cetuximab, panitumimab, aflibercept, ramucirumab) is permitted and should be administered at the investigator discretion per local practices, to the approved targeted population per label. Biological agents can be resumed for patients randomized to the Treatment Group 2 weeks after the TheraSphere administration (i.e. with cycle 2 of the standard-

of-care chemotherapy). Standard of care biological agents can start along with the first cycle of second line chemotherapy for patients randomized to the Control group.

Patients will have regular clinical study visits as long as they participate in the trial. During these visits, safety and efficacy data will be collected and recorded.

The primary efficacy endpoints of the trial will be PFS and HPFS. Once a patient has progressed, he/she will have reached the primary efficacy endpoints of the trial, but the patient will be encouraged to remain on the trial for evaluation of the secondary endpoint of survival.

Following disease progression, patients in either group may receive the Best Alternative Therapy or Care for further treatment of their disease. For patients randomized to the Treatment Group, TheraSphere will be provided to patients amenable to further treatment with TheraSphere.

8. STUDY POPULATION AND ELIGIBILITY CRITERIA

8.1 PATIENT POPULATION

Patients with metastatic colorectal carcinoma (mCRC) to the liver who have disease progression with first line chemotherapy, either an oxaliplatin-based regimen or an irinotecan-based regimen and who are eligible for second line chemotherapy with the alternative chemotherapy regimen.

8.2 ELIGIBILITY CRITERIA

Patients must meet all of the following inclusion criteria:

1. Must be a male or female, 18 years of age or older, and of any ethnic or racial group
2. If primary tumor has not been resected, it must be clinically stable
3. Must have colorectal cancer with unresectable metastatic disease to the liver (unresectable unilobar or bilobar disease) who have disease progression in the liver with oxaliplatin or irinotecan based first line chemotherapy
4. Must be eligible to receive second-line standard-of-care chemotherapy with either 1) an oxaliplatin-based chemotherapy regimen, or 2) an irinotecan-based chemotherapy regimen
5. Must have baseline efficacy images with measurable target tumors in the liver according to RECIST 1.1 using standard imaging techniques taken within 28 days prior to randomization. , Images must be taken after, or at the time of completion of first line chemotherapy
6. Tumor replacement $\leq$50% of total liver volume
7. Current ECOG Performance Status score of 0-1 through screening to first treatment on study.
8. Will have completed the first line chemotherapy regimen at least 14 days prior to the initiation of 2^{nd} line chemotherapy under the protocol
9. Patient is willing to participate in the study and has signed the study informed consent.
10. Serum creatinine $\leq$2.0 mg/dL

11. Serum bilirubin up to 1.2 x upper limit of normal
12. Albumin $\geq$3.0 g/dL
13. Must not have a history of hepatic encephalopathy
14. Must not have any contraindications to angiography and selective visceral catheterization such as bleeding diathesis or coagulopathy that is not correctable by usual therapy of hemostatic agents (e.g. closure device)
15. No history of severe peripheral allergy or intolerance to contrast agents, narcotics, sedatives or atropine that cannot be managed medically
16. Must have neutrophil count >1200/mm^3 ($1.2x10^9$/L)
17. No presentation of pulmonary insufficiency or clinically evident chronic obstructive pulmonary disease
18. No cirrhosis or portal hypertension
19. Must not have received prior external beam radiation treatment to the liver
20. Must not have received any prior intra-arterial liver directed therapy, including TACE, or Y-90 microsphere therapy
21. Must not have any planned liver directed therapy or radiation therapy
22. Must not have planned treatment with biological agents within 28 days prior to receiving TheraSphere
23. Must not have undergone any intervention for, or compromise of, the Ampulla of Vater
24. Must not have any clinically evident ascites (trace ascites on imaging is acceptable)
25. Must not have any toxicities due to prior cancer therapy that have not resolved before the initiation of study treatment, if the Investigator determines that the continuing complication will compromise the safe treatment of the patient
26. Must not have any significant life-threatening extra-hepatic disease, including patients who are on dialysis, have unresolved diarrhea, have serious unresolved infections including patients who are known to be HIV positive or have acute HBV or HCV
27. Must not have any confirmed extra-hepatic metastases. Limited, indeterminate extra-hepatic lesions in the lung and/or lymph nodes are permitted (up to 5 lesions in the lung, with each individual lesion <1 cm; any number of lymph nodes with each individual node <1.5 cm)
28. Must not have any contraindications to the planned second line standard-of-care chemotherapy regimen

29. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to randomization, and must not be breastfeeding; and must agree to use contraceptive for duration of study.

30. Must not have participated in a clinical trial with an investigational therapy within 30 days prior to randomization

31. Must not have any co-morbid disease or condition that would place the patient at undue risk and preclude the safe use of TheraSphere Treatment, in the investigator's judgment

9. STUDY VISITS, EVALUATIONS AND PROCEDURES

9.1 STUDY VISITS

Study treatment visits should occur at the time intervals outlined below and in the study visit schedule in Section 3. All study visits that take place after the screening/randomization period should occur within +/- 7 days of the designated time interval for that study visit.

9.1.1 SCREENING/RANDOMIZATION (DAYS -14 TO DAY 0)

All screening and baseline evaluations must be completed within 14 days prior to randomization except for KRAS test results. There is no time limit prior to randomization for KRAS test results. Results from standard-of-care tests and examinations taken within 14 days prior to randomization may be used to determine the patient's eligibility. Baseline images for disease evaluation must have measurable target tumors in the liver according to RECIST 1.1, be taken within 28 days prior to randomization, and be taken after, or at the time of completion of first line chemotherapy. CT scans obtained for clinical management may be used as baseline disease assessment images if they conform to the image requirements of the protocol. All patients must discontinue first line chemotherapy agents and VEGF inhibitors during the screening period. The following activities will be completed during the screening period within 14 days prior to randomization.

1. Informed Consent must be signed, as described in Section Informed Consent 13.7.
2. Patient demographic information will be collected, as described in Section 9.2.2.
3. Patient Medical History information will be collected, as described in Section 9.2.3.
4. A physical examination as described in Section 9.2.4 will be done.
5. ECOG Performance Status will be assessed as described in Section 9.2.5.
6. Medication history & Prior treatment history will be obtained as described in Section 9.2.6.
7. The estimation of liver tumor burden (must be less than 50%) will be completed as described in Section 9.2.7.
8. Baseline clinical laboratory tests including blood chemistry, hematology and coagulation tests as described in Section 9.2.8 will be done.
9. A serum pregnancy test as described in Section 9.2.9 will be administered for all female patients of childbearing potential.
10. The patient's eligibility to participate will be assessed as described in Section 9.2.10.
11. A baseline CEA level will be drawn.
12. Baseline images for disease assessment (Spiral CT/MRI of abdomen/pelvis and Spiral CT/MRI of chest) will be taken as described in Section 9.2.15.

13. Baseline Quality of Life assessments will be completed as described in Section 9.2.12.
14. Documentation of the intended second line chemotherapy regimen, including the use of biological agents and dosage.

Following Screening, patients meeting the eligibility criteria will be randomized as described in Section 9.2.13. The date of screening is the date all screening procedures are complete.

9.1.2 Q2 WEEKS FOLLOWING RANDOMIZATION

The following clinical patient management activities will be completed every 2 weeks until disease progression or discontinuation of chemotherapy and documented on the eCRF:

1. Complete appropriate clinical laboratory tests, except CEA and coagulation unless clinically required, as described in Section 9.2.8.
2. Assess ECOG Performance Status as described in Section 9.2.5.
3. Administer Chemotherapy as described in Section 9.2.14.2.
4. Record details on the clinical assessments and administration of Chemotherapy as described in Section 9.2.16.
5. Record any concurrent medications and any adverse events as described in Section 9.2.17 and 12.2.

9.1.3 Q 8 WEEKS FOLLOWING RANDOMIZATION UNTIL DISEASE PROGRESSION (+/- 1 WEEK)

Every 8 weeks following randomization until determination of disease progression, the following evaluations will be completed in addition to the activities described in 9.1.2:

1. Complete appropriate clinical laboratory tests, as described in Section 9.2.8.
2. Assess ECOG Performance Status as described in Section 9.2.5.
3. CT/MRI images will be taken for efficacy assessment as described in Section 9.2.15.
4. Quality of Life assessments will be obtained as described in Section 9.2.12.
5. CEA

9.1.4 VISITS Q 8 WEEKS FOLLOWING DISEASE PROGRESSION (+/- 1 WEEK)

Patients should continue to be followed for overall survival following disease progression. Patients remaining on the protocol following disease progression optimally should be seen at least once every 8 weeks, with the following procedures typically conducted. For those patients who are unable to come in to the clinic for routine visits, sites should maintain telephone contact or follow-up until death or the end of the study. The following procedures should be performed as clinically indicated.

1. Administer Chemotherapy as appropriate in Section 9.2.14.2.1.
2. Record details on the clinical assessments and administration of Chemotherapy as described in section 9.2.16.
3. Record any concurrent medications and any adverse events as described in Section 9.2.16 and 12.2.
4. Assess ECOG Performance Status as described in Section 9.2.5.
5. CT/MRI images will be taken for disease assessment, as described in Section 9.2.15, to support clinical care. Images taken according to standard clinical practices should be collected until liver progression
6. Quality of Life assessments will be obtained as described in Section 9.2.12.

9.1.5 PATIENT COMPLETION OR EARLY WITHDRAWAL

When a patient completes the trial or withdraws early, the following end of study assessments will be completed, as appropriate, at the time the patient exits the trial:

1. Record the date and reason for study completion or withdrawal, as listed in Section 9.2.18.
2. ECOG status as described in Section 9.2.5.
3. Record any concurrent medications and any adverse events as described in Section 9.2.17 and 12.2.
4. CT/MRI images are taken, if appropriate, as described in Section 9.2.15.
5. Quality of Life assessments will be taken as appropriate, as described in Section 9.2.12.

9.2 STUDY EVALUATIONS AND PROCEDURES

9.2.1 POTENTIALLY ELIGIBLE PATIENTS AND INFORMED CONSENT

Any patient who appears to meet the eligibility criteria may be offered the opportunity to be evaluated for participation in this clinical trial. All such patients must sign an IRB approved informed consent form, and have the opportunity to ask the Investigator any questions regarding the trial and their rights and obligations as a trial participant before any protocol related evaluations can be performed. The details regarding informed consent are described in Section 13.7.

9.2.2 DEMOGRAPHICS

Demographic data (date of birth, age, gender, childbearing potential, race, and ethnicity) will be obtained.

9.2.3 MEDICAL HISTORY

Medical history deemed clinically significant by the Investigator will be collected per body system (allergy/immunology, auditory/ear, blood/bone marrow, cardiac arrhythmia, cardiac general, dermatology/skin, endocrine metabolic, gastrointestinal, hemorrhage/bleeding, Hepatobiliary/pancreatic, infection, musculoskeletal/soft tissue, neurologic, ocular/vision, psychiatric, pulmonary/upper respiratory, renal/genitourinary, sexual reproductive function, vascular).

Diagnoses and medical history for colorectal cancer will be recorded separately from other medical history.

All on-going medical conditions and adverse events arising from treatment of those conditions present for ≥ 30 days are generally considered a part of the patient's medical history and must be recorded at baseline.

9.2.4 PHYSICAL EXAMINATION

A physical examination will also be performed, which will cover the following:

- Vital signs: heart rate (HR), respiratory rate (RR), blood pressure (BP), and temperature (T)

- Height and weight
- Head, eyes, ears, nose, and throat
- Chest
- Heart
- Abdomen
- Extremities
- Brief neurological examination (level of consciousness, orientation, sensation, and motor function)
- Genitourinary, endocrine and allergy/immunology systems

9.2.5 ECOG PERFORMANCE STATUS

ECOG Performance Status[17] will be assessed according to the following categories:

Score	Characteristics
0	Asymptomatic and fully active
1	Symptomatic; fully ambulatory; restricted in physically strenuous activity
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.
3	Symptomatic; limited self-care; more than 50% of waking hours are spent in bed
4	Completely disabled; no self-care; bedridden.

ECOG assessments may be performed remotely for those patients receiving chemotherapy outside of the clinical study site and for those patients unable to come into clinic every 8 weeks following progression.

9.2.6 MEDICATION AND PRIOR TREATMENT HISTORY

The use of concurrent medications (medications taken within 30 days of screening and during the conduct of the study) will be obtained and documented on the relevant case report forms.

Prior treatments for colorectal cancer will be recorded separately from treatments for other medical conditions.

The start and stop dates for all such prior treatments for CRC or other cancer treatments as well as prior treatment of other medical conditions should be recorded.

9.2.7 LIVER TUMOR VOLUME DETERMINATION

CT scans for the assessment of liver metastases- must include a portal venous phase. Accurate imaging and volume calculation are essential for calculation of TheraSphere dosimetry.

Using institutional standard equipment and techniques, lobar and tumor regions of interest will be drawn and the respective lobar and tumor volumes determined (a detailed discussion begins on page 1259 in Appendix 2).

Tumor replacement, expressed as a per cent of total liver volume, must not exceed 50%. This may be done based on standard practice at the clinical site for assessment (either visual or volumetric assessment).

9.2.8 CLINICAL LABS

The following clinical laboratory assessments will be completed at specified study visits during the trial. Laboratory assessments undertaken as part of standard-of-care clinical assessment may be used.

- Hematology /coagulation panel: white blood cell (WBC) count with differential, platelet count, hematocrit, hemoglobin,
- Coagulation: Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized Ratio for prothrombin time (INR)
- Chemistry panel: serum creatinine, blood urea nitrogen (BUN), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase.
- Serum CEA

9.2.9 PREGNANCY TEST

A serum pregnancy test for females of child-bearing potential will be performed at the screening visit and prior to any subsequent TheraSphere administration. Patients determined to be pregnant are not eligible to participate in this clinical trial.

Female patients of childbearing potential must be advised that they should not become pregnant while participating in this clinical trial. Adequate methods of contraception must be used by these patients while they are enrolled in this clinical trial. Patients should not be breastfeeding while participating on this trial.

9.2.10 REVIEW ELIGIBILITY CRITERIA

Data detailing Demographic, Medical History, Physical Examination, ECOG Performance Status, Medication and Prior Oncologic Treatment, Tumor and Liver volume and Clinical Labs will be reviewed against eligibility criteria to determine eligibility. The determination will be recorded on the relevant case report form (eCRF).

9.2.11 CRC TUMOR BIOMARKERS

Blood will be collected at the institution prior to and at visits following randomization to determine the baseline and subsequent CEA values.

The date and results of the KRAS status will be recorded on the relevant eCRF during the baseline evaluation.

9.2.12 QUALITY OF LIFE

A Quality of Life (QOL) instrument suitable for patients being treated for metastatic colorectal cancer (FACT-c) will be administered at study visits every 8 weeks until progression then every 8 weeks throughout the trial. The baseline QOL assessment will be obtained after the Informed Consent is signed and before the first cycle of chemotherapy is administered.

QOL assessments may be performed remotely for those patients unable or unwilling to come into clinic every 8 weeks following progression.

9.2.13 RANDOMIZATION (STUDY DAY 0)

Patients will be randomized 1:1 to study treatment, either the Control group or the Study Treatment group. Approximately 210 patients will be randomized to each protocol group. The date of screening is the date that all screening procedures are complete.

If a patient is determined to be eligible to participate in the trial, the study site will contact the central randomization office where randomization will be determined using assignment by a computer-generated randomization scheme. Upon randomization, each patient will be assigned a subject identity code consisting of the protocol number, the country code (e.g. 01), the site number (e.g. 01) and a patient number (e.g. 001).

In order to ensure that the study treatment groups are balanced, patients will be stratified at randomization based on the following:

- Unilobar vs bilobar disease
- Oxaliplatin vs Irinotecan based first-line chemotherapy
- KRAS status (wildtype vs mutant)

Prior to randomization, the investigator will decide the most appropriate treatment for his/her patient including the chemotherapy regimen, with or without biological agent that is to be given as second line treatment.

Additional factors permitting covariate analysis will be captured at randomization but will not be stratification criteria. These factors will be defined based on the planned covariate analyses.

Patients randomized to the Study Treatment group who are unable to receive their planned study treatment will continue to be followed under their assigned study group for the purpose of the intent-to-treat analysis.

If a patient being screened is found ineligible for the study, the patient will not be randomized and the reason for treatment ineligibility should be documented on the Screen Failure Log.

All patients deemed eligible for the study must have a minimum washout of 14 days from completion of treatment with their first line agents including any biological agents (such as VEGF inhibitors) prior to commencing their second line chemotherapy treatments. Additionally, patients in the Study Treatment arm must have a minimum washout period of 28 days from any biological agent prior to receiving TheraSphere.

9.2.14 STUDY TREATMENTS

9.2.14.1 THERASPHERE

TheraSphere will be administered in place of the second cycle of chemotherapy. Patients with unilobar disease will receive treatment of the diseased lobe. Patients with bilobar disease will receive treatment to both lobes separately, administered during the same treatment session. Any type of biological agent (such as VEGF inhibitors) must be discontinued for at least 28 days prior to treatment with TheraSphere.

9.2.14.2 THERASPHERE PRE-TREATMENT EVALUATION

Patients randomized to the Study Treatment group must undergo the following evaluations in order to determine eligibility to receive the TheraSphere. These tests are described in detail in Appendix 2, pages 1254-1255 and include:

- Hepatic Angiography: selective celiac and superior mesenteric arteriograms are needed to evaluate the hepatic arterial anatomy for the whole liver, as well as evaluation of potential sources of extra-hepatic blood supply to tumors. The goal is to identify, within the hepatic vascular anatomy, a catheter placement location that allows a single TS infusion throughout the lobar tumor volume without administration of microspheres to extra-hepatic structures. A technetium-99m macroaggregated albumin (^{99m}Tc-MAA) scan is used to assess the potential for shunting microspheres to the lungs as well as the potential for the deposition of microspheres to the gastrointestinal (GI) tract. Repeat ^{99m}Tc-MAA may be needed for subsequent treatments to estimate cumulative lung shunt or re-asses GI flow. Note that 3 technical factors, as discussed in Appendix 2 (time between administration of ^{99m}Tc-MAA and the scan, ^{99m}Tc-MAA particle size and the presence of free ^{99m}Tc-MAA) can lead to an over-estimation of shunting to the lungs and should be controlled.

TheraSphere should not be administered to a patient randomized to the treatment group if:

- Deposition of microspheres to the GI tract that cannot be corrected by placement of the catheter distal to collateral vessels or the application of standard angiographic techniques, such as coil embolization to prevent deposition of microspheres in the GI tract.

- Exposure of radiation to the lungs of 30 Gray (Gy) for a single infusion or a cumulative 50 Gy limit for all infusions of TheraSphere - estimated during TheraSphere dose calculation as described in Section 9.2.14.1.3.

In the event that the patient is determined not to be suitable and/or cannot be safely treated with TheraSphere, that patient should continue with the planned second-line chemotherapy treatment as described in Section 9.2.14.2.

9.2.14.3 THERASPHERE ADMINISTRATION STRATEGY

For patients eligible to receive TheraSphere, the administration strategy (choice of artery position to infuse the target vascular bed; selection of placement of coil embolization or other techniques used to prevent microsphere deposition to the GI tract) should be determined as discussed in Appendix 2, pages 1254 - 1257. Dosimetry is based on the volume of the target vascular bed supplied by the artery selected for infusion. Patients requiring coil embolization to prevent microsphere disposition to the GI tract should undergo this procedure during TheraSphere work-up.

Since the treatment approach for TheraSphere is lobar or selective, proper imaging and volume calculation is essential for dosimetry purposes. The ability to understand hepatic anatomy relies on the sound understanding of the Couinaud hepatic segments[18]. Anatomically, the middle hepatic vein separates the right and left lobes. When drawing regions of interest and calculating lobar volumes, it is the middle hepatic vein that should be used as the anatomic delineator between the right and left lobes. If the middle hepatic vein cannot be seen, then the gallbladder and its axis relative to the liver can be used. This technique assumes standard arterial anatomy with single right and left hepatic arteries. If variants are observed angiographically, for example, an accessory right hepatic artery, then accurate angiographic correlations must be performed when drawing the regions of interest for lobar or segmental lobar volumes. This will ensure that accurate volumes are obtained and 3 or more infusions are administered. The volume that needs to be used for TheraSphere dosimetry is that volume of liver that is perfused by the vessel that will be infused.

Target liver mass is determined by the positioning of the delivery catheter in the hepatic vasculature and the resulting liver area (segments) infused. Since there is considerable individual variation in hepatic vascular anatomy, the determination of target liver mass will depend on the variant encountered. The Table below presents the most commonly encountered variants with the corresponding segments associated to them.

STANDARD AND VARIANT HEPATIC VASCULAR ANATOMY AND CORRESPONDING COUINAUD SEGMENTS

Hepatic Vascular Anatomy[a]: Angiographic Findings	**Target Segments: Infusion 1[b,c]**	**Target Segments: Infusion 2**	**Target Segments: Additional Infusion**
Standard right and left hepatic arteries	1, 5, 6, 7, 8	2, 3, 4	
Replaced right hepatic with flow to medial segment left lobe	1, 4, 5, 6, 7, 8	2, 3	
Replaced right hepatic artery without flow to middle lobe, left hepatic artery with flow to medial and lateral segments left lobe	1, 5, 6, 7, 8	2, 3, 4	
Replaced left hepatic artery without flow to medial lobe	1, 4, 5, 6, 7, 8	2, 3	
Replaced left hepatic artery with flow to medial lobe	1, 5, 6, 7, 8	2, 3, 4	
Accessory right hepatic artery	6, 7	2, 3, 4	1, 5, 8
Right hepatic artery in the presence of an accessory right hepatic	5, 8	2, 3, 4	1, 6, 7
Middle hepatic artery (irrespective of origin)	1, 5 ,6, 7, 8	4	2, 3

Notes:
a) vascular anatomy subject to variation
b) assumes caudate lobe (segment 1) derives blood supply from right hepatic artery
c) caudate lobe (segment 1), right anterior lobe (segments 5/8), right posterior lobe (segments 6/7), left medial lobe (4), left lateral lobe (2, 3)

9.2.14.4 THERASPHERE DOSE DETERMINATION

The screening angiogram and ^{99m}Tc-MAA scan are used to determine lobar liver volume from CT or MRI images, to identify vascular shunting to the gastrointestinal tract requiring use of angiographic occlusion techniques and to determine the lung shunt fraction. The target dose is 120 Gy ± 10%.

Calculation of Lung Shunt Factor: Lung shunt factor is determined from the ^{99m}Tc-MAA scan using the following equation:

Lung shunt Fraction (F) = total lung counts/ (total lung+ liver counts)

Calculation of Target Liver Mass: Convert the target liver volume to mass assuming a conversion factor of 1.03g/cm^3.

Calculation of Activity required to deliver the desired dose of 120 Gy:

The amount of radioactivity required to deliver the desired target dose (120 Gy) to the selected liver target, adjusted for the estimated fraction that will be shunted to the lung, is calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}]\,[\text{Mass of Selected Liver Target (kg)}]}{50[1\text{-}F]}$$

Calculation of estimated lung radiation exposure (Gy):

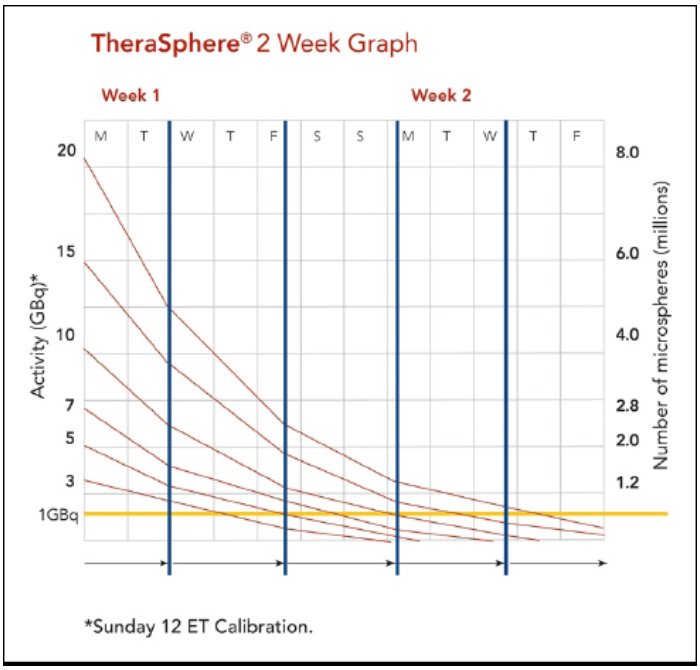
Lung Dose (Gy) per infusion = 50 * Calculated Activity in GigaBecquerel (GBq) * F

Cumulative exposure is the sum of estimated exposure per infusion for all planned infusions.

9.2.14.5 THERASPHERE DOSE VIAL SELECTION

Selection of the dose vial size to supply the required activity (GBq) for delivery of the desired target dose to the selected target liver volume via the selected vascular route is dependent on the day and time of the scheduled patient treatment and must account for the time zone in which the hospital is located and the decay in radioactivity over time. The impact of time for standard dose sizes is illustrated in the decay curve below.

The TheraSphere Treatment Window Illustrator can be used to select the appropriate dose vial or combination of dose vial(s) required to deliver the calculated activity required.



9.2.14.6 THERASPHERE ORDERING

Orders must be placed using the study-specific order form provided by the sponsor. Most standard dose vials are made to stock and can be ordered at any time per current institutional practices. Shipment will be arranged according to specified treatment time as per current practice. TheraSphere will be delivered to the institution's designated radiopharmacy and handled according to institutional practices.

Each vial of TheraSphere will be shipped with a packing slip, a copy of which must be transferred to the study coordinator for device accountability so that the vials used can be tracked to the specific infusion(s) for each patient. Disposal of used or any unused vials will be handled in accordance with hospital standard practices for disposal of radioactive materials.

9.2.14.7 THERASPHERE ADMINISTRATION

TheraSphere will be administered at a dose of 120 ± 10% Gy to each area being treated, administered in one or more selective administrations on the same day.

Patients in the Study Treatment group who have hepatic progression with hepatic lesions that are still amenable to TheraSphere are eligible for re-treatment with TheraSphere. In these cases, TheraSphere may be administered at the investigator's discretion using lobar infusions on separate treatment days.

TheraSphere should be administered by appropriately trained or designated personnel from the departments of Radiology, Nuclear Medicine, and/or Interventional Radiology.

TheraSphere administration is generally considered to be an outpatient procedure in the United States. It is generally considered to be an inpatient procedure in Europe. The physical location for after-care and recovery will be determined by individual institutional policies and facility configurations. The location and sequencing of treatment procedure may vary depending on the physical location of the angiography and nuclear medicine suites, the availability of portable gamma cameras, and the clinical judgment of the physician responsible for the treatment plan.

On the day of treatment, an arterial catheter will be placed percutaneously via the femoral or brachial artery under image guidance. The interventional radiologist performs this procedure. The patency of the catheter is maintained by an infusion of normal saline and a coagulation inhibitor (per institutional protocols) administered via a continuous infusion pump. Proper catheter positioning in the selected location in the hepatic artery will be verified on angiography before TheraSphere administration.

Standard medication protocol for sedation, pain and infection prophylaxis should be implemented per established institutional protocols. Prophylaxis with a gastric inhibitor (H2 blocker) is recommended to minimize risk of post-treatment gastrointestinal side effects. Although recommended for all patients undergoing treatment, this prophylaxis is especially important for patients undergoing TheraSphere treatment to the left lobe of the liver, due to the proximity of the gastrointestinal organs, and for patients with a prior history of peptic ulcer disease. Therapy should begin on the day of TheraSphere treatment and continue for 14-21 days following each TheraSphere treatment.

The TheraSphere Package (Appendix 1) Instructions for Use describes the specific procedure used to administer TheraSphere.

9.2.14.8 THERASPHERE ADMINISTRATION DOCUMENTATION

Any technical problems or complications related to the delivery of TheraSphere treatment to the patient must be documented in the medical record. The details of any event and its impact on the patient should be documented on an Adverse Event eCRF.

Using institutional practices, the activity of each vial of TheraSphere will be determined prior to administration. This activity will be used to calculate the actual dose delivered to the liver and lung which will be recorded on the appropriate eCRF.

Calculation of the liver dose (Gy) delivered:
Calculation of the delivered dose per infusion takes into account the activity lost to lung shunting plus activity associated with residual microspheres in the administration system and is provided by the following formula:

$$\text{Dose (Gy)} = \frac{50[\text{Injected Activity (GBq)}][1-F][1-R]}{\text{Mass of Selected Liver Target (kg)}}$$

where F = lung shunt fraction (determined in Section 9.2.14.1.3)
R = residual fraction (1-fraction of microspheres delivered)

Calculation of residual activity fraction for microspheres:
The fraction of microspheres remaining in the device is calculated using the following formula:

$$R = \frac{(W-b')}{(I-b)}$$

Where R = residual activity fraction
b = background dose rate prior to source vial measurement
I = measured dose rate of source vial positioned greater than 30 cm from ionization chamber (or other measuring device)
b' = background dose rate prior to waste measurement
W = average dose rate of shielded waste container (containing discarded vial, microcatheter, tubing) positioned with center in same location as I

Calculation of Actual Lung Radiation Exposure:
Calculation of the lung dose (Gy) delivered in each infusion is provided by the following formula:

$$\text{Lung dose (Gy)} = 50^* \text{ activity delivered (GBq)}^*F$$

9.2.14.9 THERASPHERE POST-TREATMENT PATIENT MANAGEMENT

Immediately following treatment, the patient should remain under observation consistent with institutional standard of care guidelines for aftercare in procedures involving femoral or brachial artery catheterization. These aftercare guidelines are unique and subject to the policies and procedures dictated by the respective radiology and radiation safety departments at each institution. Prophylactic treatment using gastric inhibitor (H2 blocker) should continue for 14 – 21 days post treatment. In addition, steroids (e.g., Medrol Dose Pack) may be taken (with food) over the first six days post-treatment.

Prior to discharge, patients should be instructed regarding after-care and provided with a 24-hour telephone number that they may use to contact the Site Investigator if they develop a problem or have questions about their treatment.

Any concurrent medication or therapy deemed necessary, including gastric prophylaxis, to provide adequate supportive care to the patient in the post-treatment period may be administered according to institutional standard of clinical care and should be documented on the Concurrent Medications eCRF.

9.2.14.10 RADIATION SAFETY IN THE IMMEDIATE POST-TREATMENT PERIOD

Special radiation isolation procedures for Study Treatment group patients are not necessary following TheraSphere Treatment. The existence of a small amount of long-lived radioactive byproducts in TheraSphere is a function of the production method[19]. The predominant byproducts are Y-91, Y-88 and Cr-51 with respective half-lives of 59, 107 and 28 days. The 3 year accumulated dose to the patient's liver is estimated to be 1/1000 of the planned treatment dose.

Should a patient die or require surgery in the period immediately following-TheraSphere treatment the hospital radiation safety officer should be consulted. At 60 days after the TheraSphere calibration date, a surgeon explanting a treated liver in a procedure lasting one hour would be exposed to an estimated dose to the hands of <0.6mrem. This is similar to estimated background doses from natural radiation sources which range from 0.5 to 0.8 mrem/day. Institutional radiation safety guidelines for handling of the body and/or body tissues should be followed.

9.2.14.11 SECOND-LINE CHEMOTHERAPY

The chemotherapy for this trial consists of either standard of care second-line irinotecan-based chemotherapy, or standard of care oxaliplatin-based chemotherapy.

If the patient received an oxaliplatin-based chemotherapy during first line chemotherapy, they should receive an irinotecan-based chemotherapy as their second line chemotherapy regimen under this protocol. If the patient received an irinotecan-based chemotherapy regimen during first line chemotherapy, they should receive an oxaliplatin-based chemotherapy regimen as their second line regimen under this protocol.

Generally, second-line chemotherapy is given every two weeks for 6-12 cycles. It can be continued at the discretion of the investigator. The times and doses of the cytotoxic agents administered will be recorded on the relevant eCRF.

The Control group patients will start the second line chemotherapy regimen after randomization, after the 14 day washout period from first line chemotherapy has been completed. Biological agents can start with the first cycle of second-line chemotherapy for patients randomized to the Control group.

For patients randomized to the Treatment group, one cycle of chemotherapy will be administered prior to the TheraSphere treatment. Biological agents may only be added to the chemotherapy regimen with the first subsequent cycle following the TheraSphere administration.

9.2.14.2.12 ALLOWABLE TREATMENTS FOLLOWING DISEASE PROGRESSION

After disease progression is observed and confirmed, patients in either group may receive the Best Alternative Therapy or Best Alternative Care that is considered appropriate by the investigator for further treatment of their disease. Biological agents must be discontinued for at least 28 days prior to any additional TheraSphere administration.

9.2.15 EFFICACY IMAGING – CT/MRI

Baseline disease assessment imaging scans will be obtained during screening. Images taken during the course of standard-of-care clinical management may be used as baseline images if they are taken within 28 days prior to randomization and conform to the baseline/disease assessment imaging requirements of the protocol. The baseline efficacy images must also have been taken after, or at the time of completion of first line chemotherapy. Baseline efficacy images must have measurable target tumors in the liver and be assessable according to RECIST 1.1. Efficacy assessment scans will be taken in accordance with standard-of-care clinical management guidelines every 8 weeks (+/- 1 week) post randomization until death or end of study. Most patients will be evaluated by CT images. CT scans for the assessment of liver metastases must include a portal venous phase. MRI images are also permitted. The imaging modality used at baseline must continue to be used for all efficacy images throughout the study.

Spiral CT abdomen/pelvis – must be performed with cuts of 5 mm or less in slice thickness contiguously in the axial plane. From these images, hepatic and extra-hepatic lesions will be read according to the RECIST criteria v1.1 (Appendix 3).

Spiral CT Chest – must be performed with cuts of 5 mm or less in slice thickness contiguously in the axial plane. From these images, extra-hepatic lesions will be read according to the RECIST criteria v 1.1 (Appendix 3).

All study visit CTs/MRIs taken for disease assessment (i.e. until demonstration of disease progression as determined by the Investigator plus a confirmatory scan from the next subsequent visit) must be submitted to the sponsor or designate for Centralized Review. In addition to a confirmatory scan, all efforts should be made to collect images until hepatic

progression has been confirmed. These images do not have to conform to an 8-week schedule. All disease assessment images including the baseline images must be assessable according to RECIST 1.1. Baseline images conducted in the course of standard-of-care clinical management may be used if the images conform to RECIST 1.1 and are taken after, or at the time of completion of first line chemotherapy. Images taken for clinical patient management after determination of disease progression in the liver are not submitted for Central Image Review.

A central and independent review will be done by a Central Imaging Review Organization, located in the United States (ICON Medical Imaging) designated to review the CT/MRI images. The Central Imaging Review Organization will be qualified by training and experience. All Central Image Review readings (independent reads by two radiologists with adjudication by a third radiologist) will be performed in a blinded fashion on the full set of patient images and captured on appropriate eCRF for database entry. The results of the study endpoints will be based on the Central Image Review findings.

9.2.16 STUDY TREATMENT MEDICATION RECORD

At all relevant study visits, the details of treatment administered during the study will be recorded, including the doses and start and stop times.

The addition of any treatments for colorectal carcinoma after disease progression is observed will be documented on the appropriate eCRF.

9.2.17 CONCURRENT MEDICATION RECORD

At every study visit until disease progression or 30 days after discontinuation of the last study therapy, new medications or changes in concurrent medications will be documented on the appropriate concurrent medication eCRF. Documentation will include dosage, start/stop dates, date of change of dosage and any drug holidays. After disease progression or 30 days after discontinuation of the study therapy (second-line chemotherapy alone or TheraSphere administration and second–line chemotherapy) whatever comes first, only data about anti-cancer treatments (systemic therapy or liver directed treatments) or medications given for the treatment of adverse events related to TheraSphere will be collected.

9.2.18 REASONS FOR STUDY COMPLETION/ EARLY WITHDRAWAL

In accordance with the Declaration of Helsinki, and applicable state and federal regulations, a trial subject has the right to withdraw from the study at any time and for any reason. Every effort should be made to have patients complete the study within the provisions of informed consent. However, the participation of the patient may be discontinued at any time during the study when, in the judgment of the investigator, sponsor or subject, it is appropriate. For example:

- Patient's desire for any reason to withdraw consent
- Death of the patient
- Administrative reasons
- It is considered necessary by the investigator or sponsor, for any reason

Lost to follow-up is not an adequate reason for withdrawal. Patients should be encouraged to attend study visits until completion of the study or until a decision is taken to withdraw for one of the above-noted reasons.

If the patient is removed because of intolerance to the study treatment, he/she should be under medical supervision as long as deemed appropriate by the treating physician. If the patient is discontinued due to an AE, the event will be followed until it resolves to the Investigator's satisfaction or is considered stable. The details and reasons for discontinuation must be carefully and completely documented.

10. STATISTICS

10.1 SAMPLE SIZE ESTIMATE

This study is a randomized open label multi-center Phase III adaptive trial using a group sequential design with primary endpoints of PFS and HPFS. The study could be stopped early for efficacy at an interim analysis for superiority in PFS but not HPFS.

The study is designed to detect a 2.5 months increase in median PFS from 6 months in the control arm to 8.5 months in the TheraSphere arm (i.e., hazard ratio = 0.71), and a 3.5 month increase in median HPFS time, from 6.5 months in the control arm to 10 months in the TheraSphere arm (ie, HR =0.65), using log rank tests.

The analysis of PFS will be based on a group sequential design with 2 interim analyses (at 50% and 70% of PFS events) with a stopping boundary defined by the rho family error spending function with rho=1.5 (Jennison and Turnbull, 2000[20]). It is estimated that a maximum of 420 patients will need to be recruited over 36 months, with a 1 year additional follow-up period. This includes an adjustment to take account of an assumed 10% of patients who will be lost to follow-up and for whom a date of progression or death is not recorded. The Hochberg procedure[23] will be used to control Type I error for the two primary endpoints at the final analysis.

A simulation study, assuming that PFS and HPFS have a correlation between 0.3 and 0.8, showed that the power to detect the target difference in either median PFS (ie, HR=0.71) or median HPFS (ie, HR=0.65) is >90%, and the power to detect the target difference in PFS or HPFS alone is >80%. The simulation study also demonstrated control of Type I error.

Although the forecasted accrual period has now been increased to 60 months, this does not increase the number of patients required, or affect the statistical power of the study since both the power and the timing of the interim and final analyses are based on the number of PFS events rather than the number of patients.

10.2 STATISTICAL ANALYSIS PLAN

The statistical analysis plan will be written after the final protocol is issued and will be updated, as required, in association with any protocol amendments. The plan will include tables, listings and graphs and describe statistical programming considerations.

10.2.1 POPULATIONS AND SUB-GROUPS

- **Intent To Treat population (ITT)**

All randomized patients will be analyzed according to the treatment group to which they were randomized.

- **Per Protocol Population (PP)**

All randomized patients will be analyzed according to the treatment actually received. Patients with major protocol deviations which may affect the efficacy evaluation will be excluded from the PP population.

- **Safety Analysis Population (SA)**

All randomized patients who received study treatments at least once will be included in the safety analysis.

- **Early drop-outs**

According to an intention-to-treat methodology, randomization will be performed upfront, before any further invasive tumor assessment (angiogram) or treatment planning.

10.2.2 TRIAL ENDPOINTS

10.2.2.1 PRIMARY EFFICACY ENDPOINTS

The primary study endpoints are PFS and HPFS. The study will be considered to have met its objective if at least one of the primary endpoints is statistically significant. PFS is defined as the time from randomization until progression, as defined by RECIST v 1.1, or death, and HPFS is defined as the time from randomization to the date of disease progression in the liver according to RECIST 1.1, or death. For this protocol, the minimum time from baseline to establish Stable Disease is 6 to 8 weeks, the time to complete a minimum of one set of follow-up disease assessment images from baseline. For patients who terminate the study before progression or death, patients will be censored at the date the patient is last known alive and not progressed.

10.2.2.2 SECONDARY STUDY ENDPOINTS

- Overall Survival (OS): OS is defined as the time from randomization until the patient dies.

- Time to symptomatic progression (TTSP): TTSP is defined as the time from randomization to assessment of ECOG performance status >2. Deterioration in performance status is to be confirmed at one subsequent evaluation 8 weeks later.

- Objective Response Rate and Disease Control Rate: At Baseline, target tumors are identified, read and measured for size. At all subsequent follow-up visits, the target tumor will be assessed and categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) per RECIST v1.1 at each time point. Objective Response rates at each time point and Best Overall Objective

Response Rates will be evaluated. Also, Disease Control rates at each time point and Best Overall Disease Control Rates will be evaluated.

- Quality of Life: will be assessed at all visits for enrolled patients using FACT-c.

  Safety: will be assessed at all visits for enrolled patients using v 4.0 of the National Cancer Institute's Common Terminology for Adverse Events (NCI: CTAE). All adverse events, serious adverse events, and unanticipated adverse device effects as defined by the study protocol will be collected throughout the duration of the study. These events will be documented and recorded on the Adverse Event ECRF using the NCI-CTCAE v. 4.0 standards, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

10.2.3 EFFICACY ANALYSIS

10.2.3.1 PRIMARY ENDPOINTS STATISTICAL ANALYSIS PLAN

The efficacy analysis will be performed on the ITT and PP populations. Tumor response as assessed by a central imaging laboratory blinded to treatment assignment will be used for the primary efficacy analysis. This analysis will be repeated using the investigator assessment of tumor response as a supportive analysis of PFS and HPFS.

PFS and HPFS will be compared between treatment arms using log rank tests at an overall one-sided alpha level of 0.025 to test the null hypothesis that the hazard rates for the treatment and control arms are equal versus the alternative hypothesis that the hazard rate for the TheraSphere arm is less than the hazard rate for the control arm, ie,

$$H_0: \lambda_T = \lambda_C \quad \text{versus } H_1: \lambda_T < \lambda_C,$$

where λ_T and λ_C represent the PFS or HPFS hazard rates for TheraSphere and control arms respectively. The Kaplan-Meier method will be used to estimate the PFS and HPFS curves in the two treatment arms. The hazard ratio and two-sided 95% confidence limits for the treatment effect will be presented. Log rank tests converted to z-scores will be used to compare the primary endpoints between the treatment arms.

Interim Analysis of PFS: Two interim analyses of PFS are planned to be performed by the Independent Data Monitoring Committee (IDMC) based on group sequential stopping rules using an alpha boundary defined by the rho family error spending function with rho=1.5. The first interim analysis is planned at 172 PFS events (progressions or deaths). PFS will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.372 based on the rho family error spending function, corresponding to a one-sided p-value ≤0.0088 allowing the study to be stopped early for efficacy, in which case HPFS will be tested at the same boundary as PFS using a log rank test converted to a z-score.

A second interim analysis is planned at 241 PFS events, where PFS will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.330 based on the rho family error spending function, corresponding to a one-sided p-value ≤0.0099 allowing the study to be stopped early for efficacy. If the study is stopped early for PFS at the second interim analysis, HPFS will be tested using the boundary derived based on an incremental alpha of 0.0057. This

boundary will account for the correlation between the z-score for HPFS at the first interim analysis and the z-score for HPFS at the second interim analysis, which is determined by the observed number of HPFS events at the first interim analysis and the cumulative number of HPFS events observed at the second interim analysis.

At each of the interim analyses, if the conditional power for both PFS and HPFS is less than 15% the study could be stopped early for futility, using the method described in Proschan et al (2006)[21] .

OS will also be analyzed at the interim analyses. However, no formal stopping rules will be performed based on this interim OS analysis.

Final Analysis of PFS and HPFS: The final analysis is planned at 344 PFS events. The Hochberg procedure[22] will be used to control Type I error for the two primary endpoints. Whichever of PFS or HPFS that has the larger p-value, will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.312 with a corresponding one-sided p-value ≤0.0104 required to declare a statistically significant improvement in hazard rate for this endpoint. To ensure that Type I error is controlled for both primary endpoints, this boundary is based on the incremental alpha of 0.0104 instead of the p-value scale boundary of 0.0168 using the rho family error spending function with rho=1.5.

According to the Hochberg procedure, if the primary endpoint with the larger p-value is statistically significant then the other primary endpoint is also statistically significant. However, if the primary endpoint with the larger p-value is not statistically significant then the other primary endpoint will be compared between treatment arms using a log rank test converted to a z-score and compared to the nominal critical value of 2.562 based on the rho family error spending function, with a corresponding one-sided p-value ≤0.0104/2 = 0.0052 required to declare a statistically significant improvement in hazard rate for this endpoint.

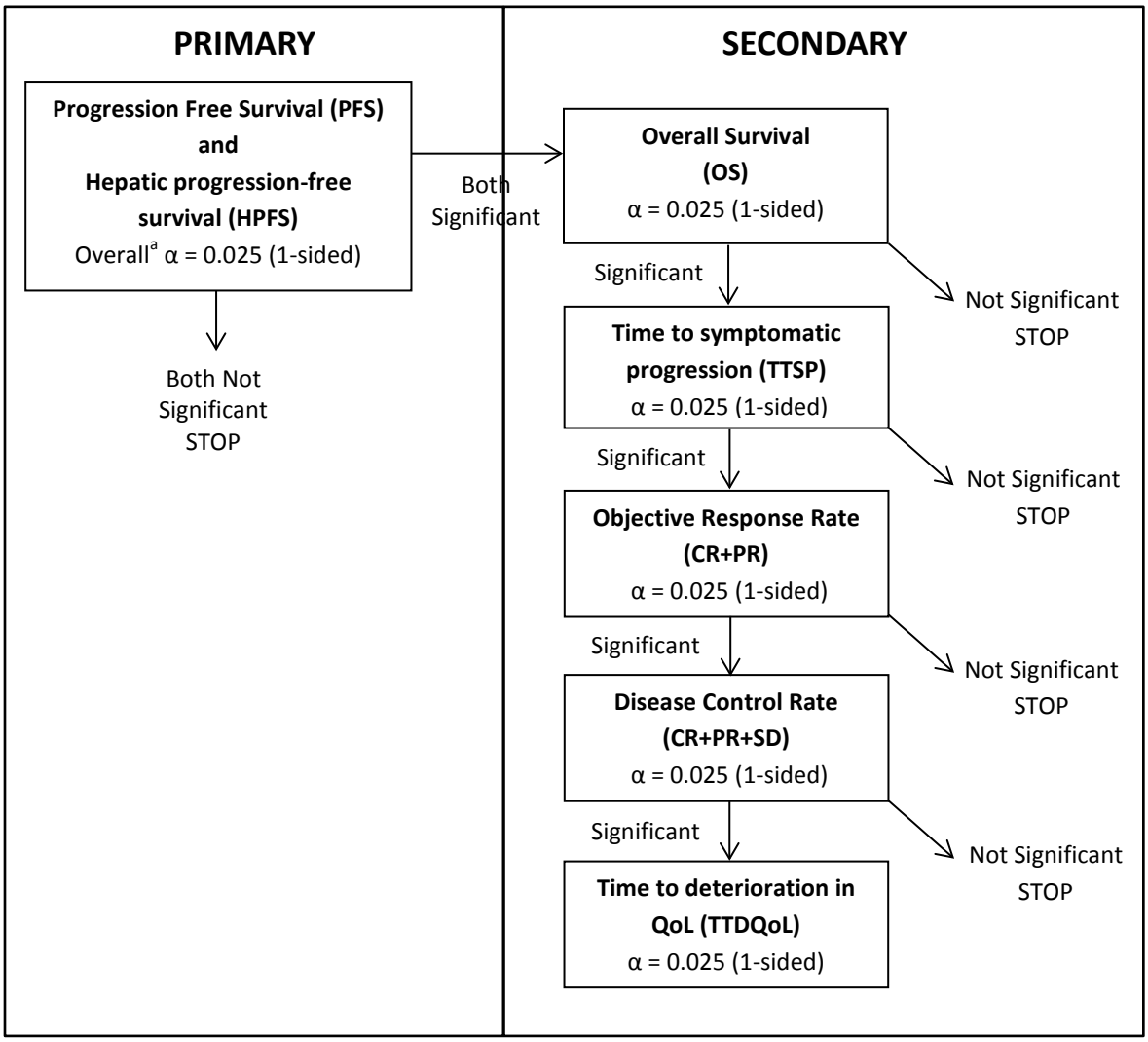
Further supportive analyses of the data using the Cox regression model may be conducted to evaluate the effect of multiple covariates, including the stratification factors.

10.2.3.2 SECONDARY ENDPOINT STATISTICAL ANALYSIS PLAN

Secondary study endpoints, with the exception of OS, will be analyzed only at the final analysis to determine the statistical significance, if any between, the Study Treatment and Control groups.

A hierarchical approach for analysis of secondary endpoints will be employed as shown in the figure below. That is, if both primary comparisons are statistically significant, the secondary endpoints will be analyzed in order of the list below and will continue as long as the obtained 1-sided probability is equal to or less than 0.025. If a probability of greater than 0.025 is obtained, the inferential analysis of secondary endpoints will stop and not proceed further down the ordered list. In this manner the overall study alpha is protected and no further adjustment for multiplicity of analyses is required.

Hierarchical approach to control study-wise Type I error of primary and secondary efficacy endpoints



[a] Type I error is controlled at α = 0.025 (1-sided) over the 2 planned interim analyses and final analysis.

- Overall Survival will be calculated as the time from randomization until death for any cause, with censoring at the date of last contact for patients alive. The Kaplan-Meier method will be used to estimate the OS curves in the two treatment arms. Comparison between the treatment arms will be performed using the log-rank test converted to a z-score, to test the null hypothesis that the OS hazard rates for the treatment and control arms are equal versus the alternative hypothesis that the OS hazard rate for the Therasphere arm is less than the OS hazard rate for the control arm , ie,

$$H_0: \lambda_T = \lambda_C \quad \text{versus } H_1: \lambda_T < \lambda_C$$

where λ_T and λ_C represent the OS hazard rates for TheraSphere and Control arms respectively.

A sensitivity analysis for OS will be performed displaying control treatment failures who go on to receive Yttrium-90 microspheres separately from controls treatment failures that do not go on to be treated with Yttrium-90 microspheres.

- Time to symptomatic progression (TTSP) will be calculated as the time of randomization to assessment of ECOG performance status>2. Deterioration in performance status is to be confirmed at one subsequent evaluation 8 weeks later. The Kaplan-Meier method will be used to estimate the TTSP curves in the two treatment arms. Comparison between the treatment arms will be performed using the log-rank test converted to a z-score, to test the null hypothesis that the TTSP hazard rates for the treatment and control arms are equal versus the alternative hypothesis that the TTSP hazard rate for the Therasphere arm is less than the TTSP hazard rate for the control arm, ie,

  $$H_0: \lambda_T = \lambda_C \quad \text{versus } H_1: \lambda_T < \lambda_C$$

  where λ_T and λ_C represent the TTSP hazard rates for TheraSphere and control arms respectively.

- Objective response rate. The response probability will be estimated in each of the two treatment arms as proportion of CR+PR (as defined by RECIST v 1.1) over the total number of ITT or PP patients. Best overall objective response rate will be compared using the continuity adjusted Newcombe-Wilson test, to test the null hypothesis that the proportions of patients achieving a ORR are equal in the treatment and control arms versus the alternative hypothesis that the proportion of patients achieving ORR is greater in the TheraSphere arm compared to the control arm, ie,

  $$H_0: p_T = p_C \quad \text{versus } H_1: p_T > p_C$$

  where p_T and p_C represent the proportion of patients achieving an objective response for TheraSphere and control arms respectively. The two-sided 95% confidence limits will be calculated.

- Disease control rate. The response probability will be estimated in each of the two treatment arms as proportion of CR+PR+SD (as defined by RECIST v 1.1) over the total number of ITT or PP patients. Best overall disease control rate will be compared using the continuity adjusted Newcombe-Wilson test, to test the null hypothesis that the proportions of patients achieving a DCR are equal in the treatment and control arms versus the alternative hypothesis that the proportion of patients achieving DCR is greater in the TheraSphere arm compared to the control arm, ie,

  $$H_0: p_T = p_C \quad \text{versus } H_1: p_T > p_C$$

  where p_T and p_C represent the proportion of patients achieving disease control for TheraSphere and control arms respectively. The two-sided 95% confidence limits will be calculated.

- Quality of Life. The total score of the FACT-c QoL instrument will be calculated, the scores of each domain and each question at each time-point and their differences from baseline will be summarized for each treatment arm. The two treatment arms will be compared applying a mixed linear model with the treatment as factors, the baseline score and the relative time from baseline as covariates. A deterioration in QoL is defined as a 7-point decline in the total score or death whichever occurs first. The time to deterioration in QoL (TTDQoL) will be calculated as the interval between the randomization date and deterioration in QoL. The Kaplan-Meier method will be used to estimate the TTDQoL curves in the two treatment arms. The treatment arms will be compared using a log-rank test converted to a z-score, to test the null hypothesis that the TTDQoL hazard rates for the treatment and control arms are equal versus the alternative hypothesis that the TTDQoL hazard rate for the TheraSphere arm is less than the TTDQoL hazard rate for the control arm, ie,

  $$H_0: \lambda_T = \lambda_C \quad \text{versus } H_1: \lambda_T < \lambda_C$$

  where λ_T and λ_C represent the TTDQoL hazard rates for TheraSphere and Control arms respectively.

Further supportive analyses of the secondary efficacy endpoints using the Cox regression model may be used to evaluate the effect of multiple covariates, including stratification factors.

10.2.4 SAFETY ANALYSIS

The safety analyses will be performed on the SA population.

All treatment emergent adverse events (TEAEs), defined as events which were not present at baseline or worsened in severity following the start of treatment, will be reported according to NCI Criteria. The incidence of TEAEs will be summarized according to MedDRA coded primary system-organ class (SOC) and preferred term (PT). The summaries will be presented overall (severity grades 1-5), for grade ≥3 events and by treatment discontinuation. These summaries will present the number and percentage of patients reporting an adverse event for each classification level as well as the number of events reported.

Serious adverse events (SAE) will be tabulated by treatment group.

Laboratory values will be summarized by treatment group over time and overall.

10.2.4.1 FEASIBILITY SAFETY ANALYSIS

After the first 20 patients in the treatment group have received TheraSphere followed by at least 2 cycles of chemotherapy, a feasibility safety assessment will be conducted. The IDMC will review the safety results of both the control and treatment groups in an unblinded fashion. The IDMC will take into consideration the established safety profiles of TheraSphere, oxaliplatin based, and irinotecan based chemotherapy, as described in the package inserts for each product as well as the published literature. The expected high rates of adverse events and death that are associated with disease progression in patients with advanced colorectal cancer will be considered.

A consideration for adjusting the dose of cytotoxic agents, or other safety recommendations, or stopping further enrollment to trial may be made by the IDMC if there is:

- an unanticipated patient death definitely or probably related to the sequential administration of TheraSphere with oxaliplatin based or irinotecan based chemotherapy
- there is a pattern of serious toxicity clearly related to the sequential administration of TheraSphere with oxaliplatin based or irinotecan based chemotherapy.

Such a toxicity pattern must be clearly different from, or more severe than, what might be expected from independent administration of the chemotherapy regimens and TheraSphere. The potential adverse impact of any such pattern of toxicity on the survival or well being of the patient should be considered in the context of the safety and outcome expectations of patients with advanced colorectal cancer. References to consider include a Phase I trial of yttrium-90 microspheres in combination with oxaliplatin[10] based chemotherapy and a Phase I trial of yttrium-90 microspheres in combination with irinotecan[11] based chemotherapy, and the experience of TheraSphere in the treatment of patients with colorectal cancer and hepatic metastases[7].

10.2.5 POOLABILITY AND OTHER ANALYSES

The number of randomized patients, the number of patients treated, the number of patients in each analysis population will be summarized. The number of patients discontinuing from active treatments and reasons for discontinuation will be summarized. In the same manner the number of patients discontinuing follow up and reasons for discontinuations will be reported.

Listings of reasons for discontinuation from active treatments, from follow up, and reasons efficacy data cannot be evaluated in the PP population will be also provided.

Duration of follow up will be described by descriptive statistics such as median and interquartile range.

Demographic, patient and disease characteristics will be listed and summarized using appropriate descriptive statistics.

Multivariate Cox regression analysis of efficacy endpoints will be conducted on stratification criteria and other factors such as age, gender, duration of disease prior to randomization to determine the impact of these factors on study endpoints.

As a sensitivity analysis, to address the poolability of data across regions, study sites and gender, a Cox regression analysis of the primary efficacy endpoints, PFS and HPFS, will be conducted including additional factors of region, study site and gender, and to determine the impact of these factors on PFS and HPFS. (NOTE: region and study site will not be included simultaneously in the model due to collinearity.) Should the impact of region, site or gender on PFS and HPFS be statistically and clinically relevant, the reasons for the observed differential treatment effect, such as patient demographic or clinical

characteristics, will be investigated and reported. If the poolability of PFS or HPFS results is in direct question as a result of this sensitivity analysis, the primary endpoints (PFS and/or HPFS) will also be analyzed separately by region, site or gender. In addition, the primary endpoints (PFS and HPFS) will be analyzed separately by US and non-US region. The specific mechanism of merging low enrolling study sites into virtual sites for purposes of analysis will be detailed in the Statistical Analysis Plan.

10.2.6 INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to oversee the conduct of the study, will follow the FDA's Guidance on IDMCs/DSMBs and comply with ISO 14155. The IDMC will meet periodically during the study to review enrollment, protocol deviations, and safety events for the study. In addition the IDMC will evaluate the data at interim analyses for consideration of stopping the study for overwhelming efficacy or futility and for sample size re-estimation at the second interim analysis. The IDMC will make formal recommendations to the study Sponsor at the time of the interim analysis and during the conduct of the study based on detailed decision rules specified in the IDMC charter. An IDMC member or designate may act as the study independent medical monitor.

11. ELECTRONIC DATA COLLECTION AND MANAGEMENT

11.1 ELECTRONIC DATA COLLECTION (EDC)

Data from this trial will be captured on electronic case reporting forms (eCRFs), and will be entered into a validated clinical database. An audit trail will be maintained to document all data changes in the database. Procedures will be followed to ensure the validity and accuracy of the clinical database.

The investigator will sign and date all indicated places on the eCRFs. This signature will indicate that thorough inspection of the data has been made and will certify that the Site Investigator has reviewed and approved the data contained on the forms.

11.2 DATA MANAGEMENT

The investigator will ensure that trial data quality is maintained to current standards of Good Clinical Practice and that data are submitted in a timely manner as outlined in the protocol and supporting documentation, including responses to data queries, until the trial is terminated.

Errors must be corrected in accordance with EDC data entry guidelines.

12. ADVERSE EVENTS

12.1 ADVERSE EVENT DEFINITIONS

Adverse experience will be considered synonymous with the term adverse event and vice versa.

12.1.1 DEFINITIONS OF AE/SAE FOR DRUGS

Adverse Event (AE)

An AE is any untoward medical occurrence or undesirable event(s) experienced in a subject or clinical investigation subject that begins or worsens following administration of the study drug, whether or not considered related to the treatment by the investigator.

An undesirable event(s) can be, but is not limited to, symptoms experienced by a subject or objective findings, such as significant clinical laboratory abnormalities.

Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening ("life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

12.1.2 DEFINITIONS OF ADE/SADE/UADE FOR DEVICES

Serious Adverse Event (SAE)

Adverse event that:

- led to a death,
- led to a serious deterioration in health that either:
    - resulted in a life-threatening illness or injury, or
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization, or
    - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Adverse Device Effect (ADE)

An adverse device effect is an adverse event (AE – previously defined) related to a medical device including device procedure and includes but not limited to any event resulting from device deficiencies such as insufficiencies or inadequacies in the instructions for use or the deployment, implantation, installation or malfunction of the device; any event that is the result of user error.

Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (SAE – previously defined).

Unanticipated Adverse Device Event (UADE)

An unanticipated adverse device effect is any serious adverse effect which by its nature, incidence, severity and outcome has not been identified in the risk assessment, the informed consent form as well as the protocol.

12.2 RECORDING ADVERSE EVENTS

All adverse events and adverse device effects will be documented from the date of randomization until disease progression or 30 days after discontinuation of the study therapy (second-line chemotherapy alone or TheraSphere and second-line chemotherapy), whatever comes first. After this, only adverse events related to TheraSphere will be collected.

In this study, patients should be encouraged to report adverse events spontaneously or in response to general, non-directed questions. At any time during the study, the patient may volunteer information that resembles an adverse event. Once it is determined that an adverse event has occurred, the Investigator should obtain all the information required to complete the adverse event form. Any medical management of an event and the date of resolution of the event must be recorded in the source document and on the appropriate case reports form(s) using medical terminology according to sponsor instructions.

For each AE, the following information will be recorded:

- Adverse event
- Serious/non-serious
- Severity
- Action taken
- Relationship to study treatment
- Expected/Unexpected
- Date and time of onset
- Date and time of resolution

An expected adverse event is any AE, the nature or severity of which is identified in the relevant Package Insert or Investigator’s Brochure.

Any AE experienced by a subject will be followed until the AE has resolved to the investigator's or physician sub-investigator's satisfaction or is considered stable. If a problem still exists, then the

investigator or physician sub-investigator at his/her discretion will ask the subject to come back to the clinic for further evaluation. Any serious adverse events should be managed as discussed in Section 12.3.

Once the subject has been discharged from the study, the investigator has no obligation to seek further follow-up with the subject in order to identify new AEs. However, if the investigator becomes aware of an SAE that has occurred following the subject's discharge from the study and the investigator considers the SAE possibly, probably, or definitely related to a study drug or device, then the investigator should report the SAE as described in the protocol.

Disease progression itself is not to be considered as an AE, but signs and symptoms that led to disease progression should be recorded. If disease progression is due to the primary cancer type than this should be stated as event term for recorded SAE.

12.2.1 CAUSALITY (RELATIONSHIP TO DEVICE) ASSESSMENT

The investigator or physician sub-investigator must indicate whether he/she believes the AE is unrelated, possibly related (reasonable possibility that the investigational device caused the AE), probably related, or definitely related to the device.

The Investigator should pay careful attention to the attribution of relation for all adverse events. Because there are many similar events between the TheraSphere and the second-line chemotherapy regimen safety profiles, judgment of relation by time of administration and patient assignment to treatment or Control group should be considered.

An adverse event becomes an adverse device effect when the adverse event is considered associated with the use of the test device if the attribution is Possibly, Probably or Definitely Related. Relation to TheraSphere (screening, procedure, embolization or radiation) is not appropriate for the Control Group. Only those events with a possible, probable or definitely related attribution to TheraSphere will subject to expedited reporting. All other events documented in the trial will be addressed through periodic clinical trial reporting in the US. In the EU all SAEs are subject to expedited reporting.

12.3 SUBMITTING EXPEDITED SAFETY REPORTS

Any SAE, SADE or UADE (defined previously) must be reported by telephone or fax to the sponsor or its designate as specified in the study procedures within 24 hours of learning of the event. In the event of an emergency, the Investigator will contact the CRO using the coordinates specified in the study procedures manual.

The SAE form provided by the sponsor should be completed and signed by the investigator or physician sub-investigator. The entire SAE form needs to be completed, if possible, to keep requests for additional information to a minimum. **Patients experiencing SAE, SADE or UADE should be followed clinically and with laboratory studies, if appropriate, until medical treatment and/or medical monitoring of the event is no longer required because the event resolves or stabilizes, returns to baseline if a baseline value is available, can be attributed to agents other than the study treatments or a referral for appropriate follow-up care has been made.**

The Investigator must promptly inform the IRB of all UADE and SAE as needed per IRB requirements. These events will be reported by the sponsor as appropriate to the regulatory authorities according to relevant jurisdictional medical device regulations. The Investigator will receive notification of these events across all study centers from the sponsor.

Each AE reported on an SAE form must also be reported in the adverse event section of the eCRF.

12.4 Periodic Safety Reporting

Adverse events will be recorded on the AE form and coded using NCI CTCAE v 4.0. The investigator or physician sub-investigator will judge the severity of each AE and whether or not it is treatment-related. All AEs that occur after randomization, including events likely to be related to the underlying disease or likely to represent concurrent illness, will be reported, including events present at Baseline which worsened during the trial.

Periodic safety reports prepared by the sponsor will be distributed across all study centers. The Investigator will be responsible for informing the IRB.

12.5 Expected Adverse Events

12.5.1 TheraSphere Adverse Event Profile

TheraSphere has been approved for the treatment of HCC since 1999. Adverse events known to be related to the device or the procedure listed in the current package insert (Appendix 1). Those adverse events identified in clinical trials investigating treatment with TheraSphere of liver lesions metastatic to non-HCC primary cancers are listed below in decreasing order of frequency.

Frequency	Description of Adverse Event (per NCI-CTCAE v 3.0)
Common - >10%	Fatigue, pain, nausea, vomiting, anorexia and laboratory value abnormalities including increased alkaline phosphatase, AST, ALT, hypoalbuminemia and lymphopenia with no clinical sequelae
Infrequent - <10%	Constipation, heartburn, weight loss, fever, ascites, muscle weakness, variations in creatinine, platelets, hemoglobin and leukocytes, GI ulcer, dyspnea, supraventricular arrhythmia, diarrhea, hypotension, insomnia, rigors/chills, sweating, distension, GI obstruction, hematoma, GI hemorrhage, pleural effusion, hyponatremia, dehydration, allergic reaction, GI other, neurology other
Rare – < 1%	Alopecia, bruising, pruritis, rash, hot flashes, dehydration, taste alteration, hemorrhage, liver dysfunction, infection, dizziness, mood alteration, sensory neuropathy, somnolence, urine color change, intraoperative injury, flu-like symptoms, tumor lysis syndrome, thrombosis, metabolic/laboratory abnormalities – neutrophils, hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesemia, lipase, lymphatics other, pulmonary other vascular other, death

In addition, the following events, which may or may not be related to the use of TheraSphere or the administration procedure, have been reported in clinical trials of treatment of primary or secondary liver cancer:

Abdominal pain, dyspnoea, abdominal distention, anxiety, blurred vision, chills, hot flashes, bladder infection, lower extremity edema, gastrointestinal stoma complication including mild pain, hepatic encephalopathy, hepatorenal failure, edema, malaise, hepatic decompensation, hepatitis, duodenal ulcer, hypertension, hypertension, aspiration pneumonia, fall, gastrointestinal bleeding, elevated CEA, elevated LDH, elevated prothrombin time, elevated BUN, bacterial sepsis, hypoglycemia, abnormal platelets and electrolyte disturbances including hypercalcemia, hyperkalemia, hypomagnesemia, hyponatremia, low serum bicarbonate and low serum chloride.

12.5.2 SECOND-LINE CHEMOTHERAPY ADVERSE EVENT PROFILE

The nature and severity of expected adverse events associated with second-line chemotherapy will vary depending in part on the drug or combination of drugs used, the dosages used and the treatment regimen. To assist in the assessment of the attribution of adverse events to one or more chemotherapy drugs, the Investigator is referred to the current package insert for the respective drug(s) administered. The following summary presents a compilation of adverse events associated with second-line chemotherapy treatment of metastatic colorectal cancer reported in the literature[6] and package inserts of the relevant drugs.

FOLFOX CLINICALLY SIGNIFICANT TOXICITY PROFILE: Severe (grade 3 or 4) events include neuropathy, diarrhea, neutropenia, thrombocytopenia, nausea/vomiting (although unlikely to be grade 3 or 4), fatigue and alopecia (grade 1 or 2). There are two types of peripheral neuropathy associated with oxaliplatin - an acute self-limiting, cold-sensitive peripheral neuropathy lasting approximately 3 days and a delayed, cumulative dose dependant sensory peripheral neuropathy which has a median time to reduction or resolution of approximately 13 weeks after cessation of oxaliplatin therapy. Rarely, some patients may experience anaphylactic reactions or laryngeal paresthesia at infusion which can be addressed through extending the infusion time from 2-6 hours or pre-medication with lorazepam. Oxaliplatin has been associated rarely with pulmonary fibrosis which may be fatal. Increases in transaminases and alkaline phosphatase have been observed with oxaliplatin.

FOLFIRI CLINICALLY SIGNIFICANT TOXICITY PROFILE: Severe (grade 3 or 4) events include diarrhea, neutropenia and thrombocytopenia and nausea/vomiting. The severity of irinotecan-induced diarrhea may be greater than that associated with oxaliplatin. The incidence of neutropenia and thrombocytopenia with FOLFIRI may be lower than that associated with FOLFOX but may include febrile neutropenia. Increased numbers of patients treated with first-line FOLFIRI, vs FOLFOX, have reported grade 3 or 4 nausea/vomiting. Alopecia (grade 1 or 2) occurs more frequently with FOLFIRI than FOLFOX. Some mild changes in liver values, including increased bilirubin, transaminases and alkaline phosphatase, unlikely to cause symptoms have been observed.

5-FU/LEUCOVORIN CLINICALLY SIGNIFICANT TOXICITY PROFILE: Diarrhea, neutropenia and mucositis are commonly associated with bolus administration of 5-FU/Leucovorin. Infusion

administrations significantly reduce the incidence of gastrointestinal and dermatological toxicities but increase the incidence of hand-foot syndrome. In some patients receiving fluorouracil there may be an increased production of tears or a brown marking on the skin following the injection vein.

OTHER ADVERSE EVENTS ASSOCIATED WITH SECOND-LINE CHEMOTHERAPY DRUGS: include decreased platelets clinically manifested as bruising or petechia, anemia, fatigue, pain, sore mouth or ulcers, hair thinning or hair loss, sensitivity to sun, loss of appetite, nail changes, skin rash (hives, pruritis, urticaria), constipation, flatulence, sweating, insomnia, edema, blurred vision, difficulty breathing or swallowing, tinnitus, allergic reaction, angina, heart pain, confusion, dizziness or unsteadiness. The impact of chemotherapy drugs on reproductive ability is unknown. Some drugs may be present in breast milk.

EGFR INHIBITOR ADVERSE EVENTS: Serious adverse events include infusion reactions (including anaphylactoid reactions, bronchospasm, hypotension, pyrexia, chills, rigors, dyspnea, angioedema, urticaria, hypertension), cardiopulmonary arrests, interstitial lung disease, pulmonary fibrosis, dermatologic toxicities (including acneform rash, pruritus, erythema, skin exfoliation, paronychia, dry skin, fissures and infectious sequelae); photosensitivity, electrolyte abnormalities including hypomagnesemia, infections and renal failure. Other adverse events include nail changes, fatigue, fever, rigors, chills, pain, dyspnea, cough, constipation, diarrhea, nausea, vomiting, steatites, mucosal inflammation, malaise, infection without neutropenia, insomnia, confusion, anxiety, depression. As with all therapeutic proteins, there is a potential for immunogenicity. Increased toxicity with combination chemotherapy has been noted with pantitumamab which should be administered as monotherapy.

13. INVESTIGATOR AND SITE QUALIFICATION AND OBLIGATIONS

13.1 STUDY SITE AND INVESTIGATOR QUALIFICATION

This study will be performed by qualified investigators at multiple research centers in the United States, Canada, Europe, and Asia.

All participating study sites will be reviewed by the study Sponsor or designee in order to verify that they are able to conduct the trial. Each participating institution must have an established IRB and clinical protocol review process in compliance with the appropriate regulations (21 CFR 56 or ISO 14155) so the clinical protocol can be adequately evaluated and approved at the institutional level.

The institution must have appropriately qualified investigators, and clinical and administrative support staff in place to adequately conduct the trials according to GCP in general, and must have adequate expertise and staff in the treatment of patients with colorectal carcinoma and the ability to adequately conduct clinical research under Good Clinical Practice Standards (GCP) consistent with the regulations of 21 CFR 812, Investigational Device Exemptions, and ISO 14155.

In addition, all participating study sites must be appropriately experienced in the use of Y-90 microspheres for the treatment of liver tumors, and must have completed adequate training in order to use the TheraSphere Y-90 microsphere product. The required training will be specified by the sponsor. Generally, an adequate level of experience consists of a minimum of 5 TheraSphere administrations for sites without radioembolization experience and at least 3 administrations of TheraSphere for sites experienced with a different radioactive microsphere product.

13.2 INSTITUTIONAL APPROVAL AND DOCUMENTATION OF THE PROTOCOL

Prior to initiating the clinical study, each participating institution must have documentation that the Institution Review Board (IRB) has reviewed and approved the protocol and the Informed Consent Form (ICF).

The final IRB approved protocol, consent form, documentation of IRB approval of the consent and protocol, Study Contract, Statement of Investigator, CVs of all investigators and study coordinators, records of protocol training, and all other study-related required regulatory documentation as described in the Sections below must also be maintained in the clinical study files for this trial.

The Site Principal Investigator is ultimately responsible for ensuring that required study documentation has been obtained, that all study procedures are properly followed, and that all enrolled patients meet the eligibility criteria prior to enrollment under this protocol.

The Investigator is responsible for submission of the protocol, informed consent form, any patient education materials, and any recruitment or advertising materials and the institution's IRB.

- Written approval of the protocol and Informed Consent Form must be obtained prior to recruitment of patients into the trial at each site and prior to administration of protocol treatment to any randomized patient.
- Written approval of the recruitment and advertising materials must have IRB approval before use.
- The Investigator is responsible for obtaining and maintaining IRB approval at his facility and providing copies of all IRB correspondence to the Sponsor or designee.

This protocol is a multi-center protocol and as such must remain consistent with all other sites.

13.3 REGULATORY DOCUMENTS

The following documentation must be obtained before study enrollment can begin (with the exception of Final Report).

- Institutional Review Board Approval

A copy of the protocol and any amendments, the proposed informed consent form (ICF), other written subject information and any proposed advertising material must be submitted by the Investigator to the IRB for written approval. A copy of the written approval of the protocol and ICF

must be received by the sponsor or designee before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IRB of deviations from the protocol and SAEs as required by local procedures.

The investigator will be responsible for updating the IRB about the status of the trial at least annually and obtaining any required approvals renewal throughout the duration of the study. Copies of any correspondence and other documentation between the investigator and the IRB must be retained as part of the site documentation of the study. Copies of all such documents must be sent to the sponsor or designee.

- Institutional Review Board Membership Roster

The investigator must submit a complete and current roster of the IRB to the sponsor (Biocompatibles) or designee. Some institutions, on grounds of confidentiality, may not release the IRB roster. In such instances, the institution's General Assurance Number, assigned by the Department of Health and Human Services, is an acceptable substitute.

- Statement of Investigator

The investigator will be required to sign and date a Statement of investigator form provided to them by the sponsor or designee. A copy of this form will be given to the investigator for their files. The original form will be maintained by the sponsor or designee.

- Curriculum Vitae

The investigator will provide the sponsor or designee with his/her up-to-date curriculum vitae and those of any sub-investigators or staff personnel with significant trial responsibilities.

- Laboratory Certification and Normal Values

The Investigator will provide the sponsor or designee with the name and location of the clinical laboratory to be utilized for determination of laboratory assays, copy of certification and a list of the normal range of values of all laboratory tests. Any changes in laboratory, certification or normal ranges will be communicated promptly to the sponsor or designee or designee.

- Financial Disclosure

Financial disclosure statements will be completed for the investigator and all sub-investigators to disclose potential conflicts of interest (per 21 CFR 54 and ISO 14155). The investigator is responsible for ensuring completed and signed financial disclosure forms, which are provided by the sponsor or designee. A copy of the form(s) will be given to the investigator for their files. The original form(s) will be maintained by the sponsor or designee. Financial disclosure information will be collected by the sponsor before the start of the study and maintained for one year after study completion.

- Final Report

Upon completion of the clinical trial, a final study report will be provided by the sponsor; The Investigator will prepare and submit to the IRB a final report, including final study report.

13.4 SOURCE RECORDS AND STUDY DOCUMENTATION

Investigators are required to prepare and maintain adequate source documentation. Source documentation includes:

- documents relative to the patient's medical history that verify the eligibility criteria
- records covering the patient' participation in the study which include but are not limited to basic identification information, results of physical examinations and diagnostic tests, therapy, device administration, concurrent medication information and visit/consult notes.)

The Investigator will initial and date all laboratory reports or initial and date statements at each study visit that all clinical laboratory data was reviewed.

Federal regulations concerning the period during which study records must be maintained by the Investigator vary from country to country. Investigators are required to comply with their local regulatory authority for storage of study documentation. For the purpose of this study the minimum retention for Study Documentation is a period of two (2) years after the later of the following: (a) date on which the Study is terminated or completed; or (b) date records are no longer required to support a premarket approval application, notice of completion of a product development protocol, or other application for research or marketing permit.

Completed eCRFs that are dated and signed by the investigator must be made available for review and retrieval by the sponsor or designee at the time the subject completes the study. The sponsor or designee will provide the investigator with a copy of completed eCRFs for their files.

In order to ensure the accuracy of data collected in the eCRFs, it is mandatory that representatives of the sponsor, as well as representatives of a regulatory agency (e.g. Food and Drug Administration) or the institutional review board (IRB), have access to source documents (i.e., subject records, subject charts, and laboratory reports). During the review of these documents, the anonymity of the subject will be maintained with strict adherence to professional standards of confidentiality. The sponsor reserves the right to terminate the study for refusal of the investigator to supply source documentation of work performed in this clinical trial.

13.5 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with standard operating procedures of the sponsor or designee, which are designed to ensure adherence to good clinical practice (GCP) guidelines as required by the following:

1. World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and as amended at subsequent WMA General Assembly meetings.

2. E6 Good Clinical Practice: Consolidated Guidance (International Conference on Harmonization of Pharmaceuticals for Human Use [ICH], April 1996 governing drugs and ISO 14155 governing devices.
3. Title 21 of the Code of Federal Regulations (21 CFR) Parts 50, 54, 56, and 812.

13.6 RESPONSIBLE CONDUCT OF RESEARCH

The Sponsor will ensure that this trial is conducted in full conformity with the current revision of the 'Declaration of Helsinki", ISO 14155, the U.S. Code of Federal Regulations 21 CFR 812, and applicable state and federal regulations, whichever affords the greatest protection to the patient. The Sponsor is responsible for providing monitoring oversight for the study to ensure the involvement of the Investigator in the trial, to ensure the rights, safety and well-being of the patients, compliance to the protocol and to all applicable laws, and to oversee the completeness, accuracy and consistency of the data collected in support of a pre-market approval application in the United States.

The procedures defined in the protocol and the eCRFs will be carefully reviewed by the Sponsor with the Investigator and staff prior to time of trial initiation to ensure appropriate interpretation and implementation. No deviations from the protocol may be made without advance approval from the sponsor and the IRB as required by the policies of the IRB.

Monitors from the Sponsor, or their designees, will periodically visit the site to review case report forms, the Regulatory Binder, patient medical records including electronic records, imaging files, laboratory reports, device accountability, site training and authorization of delegation and any other records related to the study conduct. Investigator will maintain and release the records for review, provide access to the records and copies as needed, and will meet with the monitor as needed to discuss study progress and needs. The Investigator should maintain the files suitable for inspection at any time by a trial monitor from the sponsor or designee, or the appropriate regulatory authority, or designate representing these organizations.

13.7 INFORMED CONSENT

An IRB approved signed informed consent form (ICF) must be obtained from a patient before that patient can enter the trial, and before any study related evaluations can be performed on that patient.

The investigator is responsible for the creation of the ICF and must ensure that the informed consent adheres to the U.S Code of Federal Regulations, 21 CFR 50, ISO 14155 or equivalent, as appropriate to his/her country. The Investigator will ensure that the local IRB has approved the protocol and the informed consent prior to the initiation of the trial. The signed informed consent from each patient must be kept in the patient's study file.

The investigator or designee will review the treatment plan with the patient and the patient will have an opportunity to ask questions regarding study procedures, the required visit schedule, risks/benefits of the use of the device (TheraSphere), and alternative treatment options prior to signing the ICF. The patient will receive a copy of the signed informed consent to keep for their

records. Periodically during the study, revisions to the informed consent form may be needed. Patients will be informed of such revisions and any revisions must be signed and kept in the patients study file.

The acquisition of informed consent should be documented in the subject's medical record and the ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily by the investigator).

Patients for whom English is not their first language may need a written translation of the document and/or a patient advocate, according to the policies of the IRB. The Investigator will provide the sponsor or designee a copy of the IRB approved translation, if any.

13.8 PATIENT MEDICAL RECORDS

The Investigator must maintain adequate medical records regarding their care of the patient, including case histories, to support the clinical data in the case report forms. These records must be maintained and made available for monitoring and auditing by the Sponsor, or their designee, and the appropriate regulatory agency. All CT/MRIs will be maintained or archived along with the medical chart for review for at least 2 years after pre-market approval of the device.

13.9 PATIENT PRIVACY AND CONFIDENTIALITY

All collected patient data will be treated confidentially and identified only by a patient identification number. Medical records relating to this trial, including those that are electronically maintained and those that may contain information that would identify an individual patient will remain confidential, but may be reviewed by, released, and/or transmitted to representatives of the hospital, the appropriate regulatory agency, Biocompatibles (the Sponsor) or its agents, and the Independent Data Monitoring Committee when reasonable and appropriate for the conduct of the trial.

As part of the required content of the informed consent, the patient must be informed that his/her records will be reviewed by Biocompatibles and/or a representative of the appropriate regulatory agency and the Independent Data Monitoring Committee. The informed consent or related document will also state that patient privacy will be maintained pursuant to the Health Insurance Portability and Accountability Act (HIPAA), 21 CFR 21 or equivalent for countries other than the United States. Should access to the medical record require a separate HIPAA waiver or authorization per institutional confidentially policies, it is the Investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the trial.

13.10 ADDITIONAL INVESTIGATOR RESPONSIBILITIES

Additional Investigator responsibilities are noted in ISO 14155 in Section 11 of the US 21 CFR 812.100, 812.110 and in country-specific guidelines and laws and responsibilities for reporting of unanticipated adverse device events and deviations from the investigational plan per 812.150 as well as the following:

- Ensure compliance with institutional and appropriate relevant jurisdictional Radiation Safety policies and procedures.

- Assemble and coordinate a team that includes a designated co-investigator in all of the medical disciplines necessary for the efficient conduct of the protocol (oncology, interventional radiology, nuclear medicine, diagnostic radiology, etc).

- Provide a trial coordinator who will be responsible for assisting the Investigator in meeting data collection and reporting requirement and for scheduling, management and follow-up of trial patients.

- Provide adequate access to study materials for the sponsor or designee to monitor the trial at appropriate and convenient intervals and provide an adequate, secure area, within the study site facility for a sponsor or representative to conduct these monitoring activities.

14. PROTOCOL DEVIATIONS

It is vital to the success of the study that the investigator adheres to the details of the protocol. A protocol deviation is any change, divergence or departure from the study protocol in any section related to patient regardless the consequences to the patient or study outcomes.

A minor protocol deviation is defined as a divergence from the protocol that is without significant consequences to the patient and the study data. An example is missing a visit window because a patient is traveling.

A major protocol deviation is defined as a divergence from the protocol that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare, example:

- Enrollment deviations
- Eligibility criteria deviations
- Inadequate informed consent
- Intentional repeated deviations from the protocol
- TheraSphere Administration deviations: TheraSphere treatment dose outside the range of 120 Gy ± 10% (i.e. 108-132 Gy)

15. STUDY MONITORING

The study will be monitored by qualified personnel from the sponsor or a contract research organization (CRO) contracted to provide such monitoring by the sponsor. Data management and statistical analyses will be the responsibility of the sponsor who will contract with one or more organizations to manage these functions.

Before initiation of the trial, representatives from the sponsor will, together with the investigator, review the protocol and the facilities. At trial initiation, the sponsor's representative will thoroughly review the protocol and go over the eCRFs and electronic data entry procedures with the investigator(s) and other authorized staff.

During the course of the trial, a study monitor or other authorized representatives of the sponsor will visit the investigator at suitable intervals. The purpose of these visits will be to verify compliance with applicable government regulations and adherence to the protocol, ensure correct completion of the eCRFs.

In order to perform his/her role effectively, the study monitor(s) must be given access to source documentation (eg, clinic charts, original laboratory records), which support data on the eCRF, and informed consent forms. The monitor must be able to verify data appearing in the eCRFs against data in the subject's clinic chart (eg, chart notes) or in printout forms (eg, laboratory results).

16. STUDY TERMINATION

Biocompatibles reserves the right to discontinue this study for administrative reasons at any time. The end of the study is defined as the reaching of the required number of PFS events and all TheraSphere treated patients have been followed-up for a minimum of 30 days from the last TheraSphere treatment, and all treated patients in the control arm have been followed-up for a minimum of 30 days after the second cycle of second line chemotherapy.

17. APPENDICES

1. TheraSphere Product Labeling
    a. US Package Insert
    b. CA Package Insert
    c. EU Instructions for Use

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4. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN guidelines™) Colon Cancer v.2.2011, pages COL-7 and COL-C 1-6.

18. REFERENCES

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