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A Traditional Feasibility study of Gemcitabine, Cisplatin, and ^{90}Y TARE for Unresectable Intrahepatic Cholangiocarcinoma

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TABLE OF CONTENTS

DEFINITIONS OF TERMS USED

2HG	2-hydroxyglutarate
5FU	5-fluorouracil
ADC	apparent diffusion coefficient
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANC	absolute neutrophil count
BSA	body surface area
BMP	basic metabolic panel
CBC	complete blood count
CMP	complete metabolic panel
CR	complete response
CRF	case report form
CT	computer-assisted tomography
CTCAE	Common Toxicity Criteria adverse event
CTO	Clinical Trials Office
CTSA	Clinical and Translational Science Award
CTRC	Clinical and Translation Research Center
DLT	dose limiting toxicity
DSMC	Data Safety Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
HCC	Hollings Cancer Center
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICC	intrahepatic cholangiocarcinoma
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board

LTF	liver function test
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MUSC	Medical University of South Carolina
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	overall survival
PI	Principal Investigator
PFS	progression free survival
PLT	platelet count
PPI	proton pump inhibitor
PR	partial response
RECIST	Response Evaluation Criteria in Solid
REDCap	Research Electronic Data Capture
SAE	serious adverse event
SD	stable disease
SIS Unit	Sponsor-Investigator Support Unit
TACE	transarterial chemoembolization
TiTE-CRM	time-to-event continual reassessment method
ULN	upper limit of normal
^{90}Y TARE	trans-arterial embolization with Yttrium-90

PROTOCOL SUMMARY

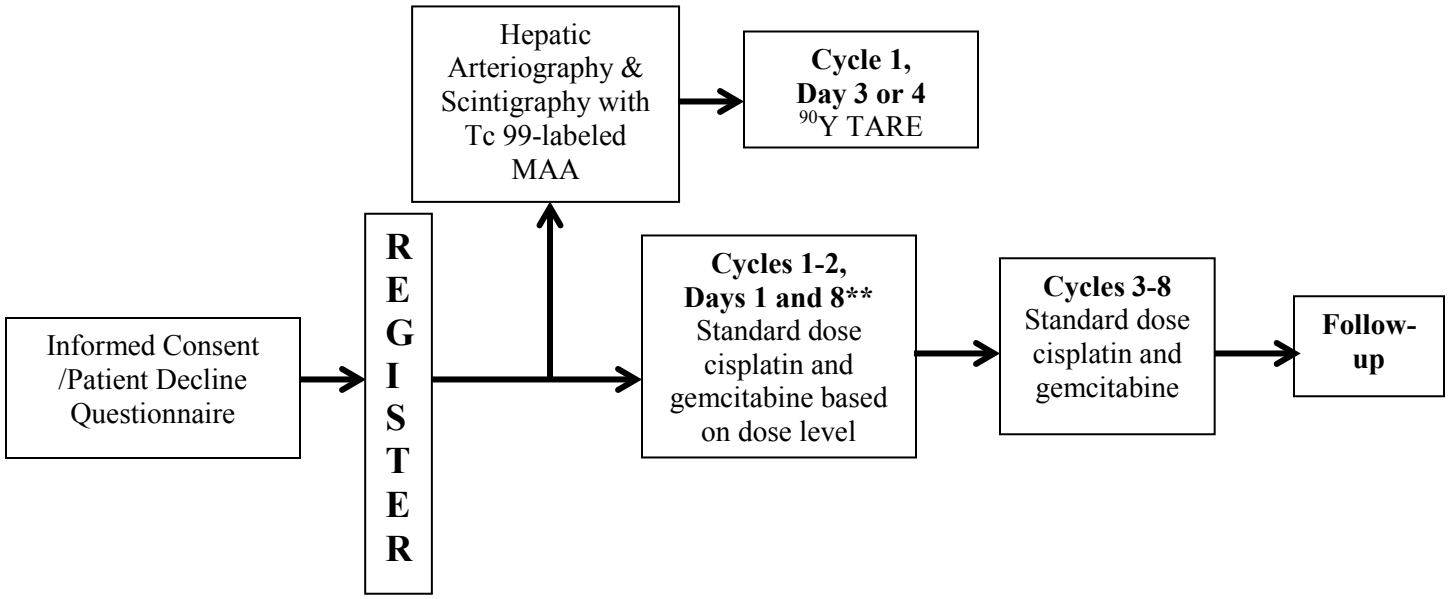
Patient Eligibility:

- Histologic diagnosis of ICC that is deemed unresectable by a multidisciplinary team that includes a hepatobiliary surgeon.
- No prior liver radiation therapy or immunotherapy for ICC.
- Only previous single agent chemotherapy for ICC allowed.
- Child-Pugh A
- Age $\geq$ 18
- ECOG performance status 0-2
- Patients must not have any grade III/IV cardiac disease as defined by the NYHA Criteria, unstable angina pectoris, or myocardial infarction within 6 months of registration. Patients with a history of myocardial infarction or irregular heart rate within 6 months prior to registration should be evaluated by a cardiologist prior to trial entry.

Required Laboratory Values:

- ANC $\geq$ 1.5K/CUMM
- PLT $\geq$ 100K/CUMM
- AST, ALT, and Alk Phos $\leq$ 5 x ULN
- Total Bilirubin $\leq$ 2.0mg/dL
- Creatinine $\leq$ 1.5mg/dL

SCHEMA



1 OBJECTIVES

1.1 PRIMARY OBJECTIVE:

To determine the safety and MTD of ^{90}Y TARE in combination with gemcitabine and cisplatin in patients with unresectable intrahepatic cholangiocarcinoma. The MTD is defined as the dose with dose limiting toxicity probability of no more than 0.25.

1.2 SECONDARY OBJECTIVES:

- To determine progression free survival.
- To determine if changes in ADC on MR predict overall survival in patients treated with chemotherapy and ^{90}Y TARE.
- To determine the response to the combination of chemotherapy and ^{90}YTARE based on molecular subtype of ICC.
- To determine if GGT level at diagnosis and after treatment is predictive of overall survival.

2 BACKGROUND

Intrahepatic cholangiocarcinoma is an uncommon malignancy affecting between 5000 to 8000 individuals a year in the United States with an age-adjusted incidence of 0.73 per 100,000 (1,2). Complete surgical resection is the only established curative treatment for ICC, but most patients present with locally advanced disease and only a third are candidates for resection. Even among patients who undergo resection, two thirds will have a recurrence with the predominate pattern of recurrence being in the remnant liver (3). Five year survival in surgical series reporting outcomes for resection of ICC range from 25-40% (4). Therapeutic options are limited in patients who have unresectable disease at presentation or recurrence not amenable to further surgery.

2.1 CHEMOTHERAPY IN BILIARY TRACT TUMORS

Different chemotherapy regimens were used for cholangiocarcinoma in the 1980's, 1990's and early 2000's, but no randomized controlled trial showed a survival benefit. The majority of these regimens contained 5FU with response rates typically from 20 to 30% and median survival from 6 to 9 months (5-11). Gemcitabine also began to be used in biliary tract cancer due to its activity in pancreatic cancer in which an overall survival benefit was seen when compared to 5FU(12). Two small phase II trials suggested that gemcitabine may have activity in biliary tract tumors. Response rates were modest at 15 to 20% with overall survival of 6.5 to 7.5 months (11,13).

2.2 ESTABLISHMENT OF CISPLATIN AND GEMCITABINE AS FIRST LINE THERAPY

Cisplatin and gemcitabine were known to be effective together in several tumor types, including head and neck, lung, and bladder cancers (14-16). For this reason, the Upper Gastrointestinal Cancer Clinical Studies Group of the United Kingdom National Cancer Research Institute designed a randomized phase II trial comparing cisplatin and gemcitabine to gemcitabine alone (the Advanced Biliary Cancer [ABC]-01 trial). Eighty-six patients were enrolled with improvement in 6 month progression-free survival from 47.7% to 57.1% (17). This study was then extended into a randomized phase III study, the ABC-02 trial. This trial established cisplatin plus gemcitabine as the standard frontline therapy for locally advanced or metastatic biliary cancer with a median overall survival 11.7 months compared to 8.1 months in the gemcitabine alone arm. Median progression-free survival was improved from 5 to 8 months in the cisplatin and gemcitabine arm. Grade 3 to 4 toxic effects were similar in both arms at 70%, but the combination arm had significantly less liver toxicity at 16% versus 27%. This was thought to be due to better control of the disease in the liver (18). There were eighty patients with intrahepatic cholangioarcinoma on this trial and the hazard ration for death was 0.57 in the combined arm. In addition, a small randomized phase III trial with eighty-four patients was also performed in Japan comparing gemcitabine and cisplatin to gemcitabine alone in patients with biliary tract cancer. Median survival was improved from 7.7 to 11.2 months with no significant increase in toxicity (19).

2.3 YTTRIUM-90 RADIOEMBOLIZATION IN ICC

Liver directed intra-arterial therapies have also been investigated in unresectable ICC. Trans-arterial embolization with Yttrium-90 tagged to glass or resin microspheres were initially used in unresectable colorectal cancer liver metastases as well as for the palliative treatment of hepatocellular carcinoma. An initial pilot study of 24 patients with ICC treated with 48 administrations of Y90 to hepatic segments or lobes demonstrated that the therapy was well-tolerated with a response rate of 86% and median survival of 14.9 months (20). Grade 3 liver toxicity was seen in 21% of patients, all in patients who had progression and one patient (4%) developed grade 4 gastrointestinal toxicity with a bleeding gastroduodenal ulcer requiring surgery. Several other series have found a median survival of 9.3 months to 22 months after Y90 for ICC (21-24).

2.4 YTTRIUM-90 TARE AND CHEMOTHERAPY

Combination chemotherapy and ^{90}Y TARE has also been investigated for colorectal cancer liver metastases. A phase I study combined FOLFOX4 chemotherapy with ^{90}Y TARE in patients with colorectal liver metastases who had not received chemotherapy for metastases. Oxaliplatin was dose reduced for the first three cycles and ^{90}Y TARE was given on the third or fourth day of the first cycle. The starting oxaliplatin dose was then increased in cohorts and 60mg/m^2 was found to be the maximum-tolerated dose for the first three cycles (25). One phase III trial randomized 44 patients with liver-limited metastatic colorectal cancer refractory to standard chemotherapy to protracted infusion 5FU alone versus in combination with ^{90}Y TARE on cycle 1, day 1. There was no increased toxicity with the addition of ^{90}Y TARE and time to liver progression was significantly improved from 2.1 months to 5.5 months (26). The SIRFLOX trial is evaluating FOLFOX6m chemotherapy alone versus in combination with ^{90}Y TARE on cycle 1, day 3 or 4 in patients with colorectal liver metastases as front line therapy and has completed accrual with over 500 patients. Analysis is pending, but safety data on the first 120 patients have shown no increased toxicity over FOLFOX6m chemotherapy alone. In addition, the FOXFIRE trial is investigating 5FU, oxaliplatin, and folinic acid chemotherapy alone versus in combination with^{90}Y TARE for patients with colorectal liver metastases in the United Kingdom.

2.5 ASSESSMENT OF RESPONSE IN ICC

Response rates to ^{90}Y TARE are 50% to 88%, but there are multiple criteria that have been used to assess response. RECIST does not correlate with survival in patients treated with Y90, but the mRECIST and EASL criteria do correlate with survival (27,28). In ICC patients treated with TACE, percent tumor necrosis and volumetric changes in ADC on MRI have been noted to correlate with survival, but these have not been assessed in patients receiving ^{90}Y TARE (28,29).

2.6 MOLECULAR SUBTYPES OF ICC

Little is known about the molecular pathogenesis of ICC and no molecular targeted agents have been approved for cholangiocarcinoma. Recently, genomic profiling of surgical specimens from patients with ICC has allowed some characterization of this malignancy with two distinct groups with different prognosis, the proliferation and inflammation classes. Mutations are common and can be found in KRAS, BRAF, IDH1, IDH2, EGFR among others (30,31). These genomic classifications have largely been performed on surgical samples from patients undergoing resection so there is no prospective data on how the genetic profile impacts response to chemotherapy or TARE. There are currently no standard serum markers to assess response to treatment in patients with ICC. One recent study found that serum GGT elevation was correlated with poor prognosis, but it is unknown if tumor response can be followed by GGT serum levels or if they are elevated in specific molecular subtypes (32). An additional study found that serum 2HG was elevated in patients with IDH1/2 mutations and that the serum level seemed to be correlated with disease burden in a small cohort (33).

2.7 SUMMARY

Gemcitabine and cisplatin chemotherapy is the current standard for the treatment of unresectable intrahepatic cholangiocarcinoma. ^{90}Y TARE combined with the current standard may be an ideal way to improve disease control in the liver as almost all patients die from their disease in the liver. The data from this trial would then be used to move to a phase II trial to determine efficacy to see if a phase III trial would be warranted. In addition, assessment of the molecular classification of intrahepatic cholangiocarcinoma could determine if there is difference in survival with chemotherapy and ^{90}Y TARE. Finally, MRI before and after treatment will be used to determine if utilizing the percent increase of mean ADC correlates with survival.

3 PATIENT SELECTION

3.1 INCLUSION CRITERIA

1. Histologic Documentation: Core needle biopsy or surgical specimen that confirms ICC. Patients must be determined to be unresectable by a multidisciplinary team that includes a hepatobiliary surgeon.
2. Prior treatment:
   - No prior liver radiation therapy or immunotherapy for cholangiocarcinoma.
   - Only one previous single agent chemotherapy for ICC allowed.
   - Patient may have prior liver resection.
3. Age $\geq$ 18 years of age.
4. ECOG performance status $\leq$ 2 (see Appendix E)
5. Child- Pugh score of A (see Appendix F)
6. Life expectancy of greater than 4 months
7. Patients must have normal organ and marrow function as defined below:

ANC	$\geq$ 1.5 K/CUMM
PLT	$\geq$ 100 K/CUMM
Bilirubin	$\leq$ 2.0 mg/dL
Creatinine	$\leq$ 1.5 mg/dL
AST, ALT, & Alk phos	$\leq$ 5 X ULN
INR	$\leq$ 2.0

8. All patients must be informed of the investigational nature of this study and must have the ability to understand and the willingness to sign a written informed consent document.
9. Willingness to use effective contraceptive methods during the study. Female patients may participate if patient is either not of childbearing potential (defined as postmenopausal for > 1 year or surgically sterile) or is practicing two forms of contraception. Sexually active male participants must agree to use a physical barrier method (male latex rubber condom with or without spermicide).
10. Patients with well controlled HIV infection are eligible if their CD4 count is >499/cu mm and viral load is < 50 copies/ml.
11. Pre-certification for the ^{90}Y TARE should be performed prior to enrollment on this study.

3.2 EXCLUSION CRITERIA

1. Patients who have had major surgery within 4 weeks prior to study registration or those who have not recovered from complications from a surgery more than 4 weeks prior to registration.
2. Patients may not be receiving any other investigational and/or anti-cancer agents.
3. Patients must not have any grade III/IV cardiac disease as defined by the NYHA Criteria (See Appendix G) unstable angina pectoris, or myocardial infarction within 6 months of registration. Patients with a history of myocardial infarction or irregular heart rate within 6 months prior to registration should be evaluated by a cardiologist prior to registration.
4. Patients must NOT have liver disease such as cirrhosis or sever hepatic impairment as defined by Child-Pugh Class B or C (See appendix F)
5. Pregnant women are excluded from this study because ^{90}Y TARE is a radioisotope agent with the potential for teratogenic or abortifacient effects. Because there is an unknown

but potential risk for adverse events in nursing infants secondary to treatment of the mother with cisplatin and gemcitabine, breastfeeding should be discontinued.

3.3 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 PATIENT REGISTRATION

The SIS Unit will provide patient registration services for the study. The SIS Unit will conduct a patient eligibility audit review of all eligibility source documents prior to patient registration. These procedures are outlined in the Investigator Initiated Trial Operations Manual. After obtaining signed informed consent and completion of required baseline assessments, eligible subjects will be registered. A unique subject number will be assigned to each patient. The SIS Unit will issue a patient registration confirmation email to the enrolling study team at the time of registration. This confirmation will include the patient's assigned cohort dose level and study ID number. Patient registrations may occur between 8AM and 5PM EST, Monday through Friday.

Prior to any study specific activities, the patient must be aware of the nature of his/her disease and willingly consent to the study after being informed of study procedures, the experimental therapy, possible alternatives, risks and potential benefits. IRB approval of this protocol and accompanying consent is required.

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the PI. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The SIS Unit should be notified of cancellations as soon as possible.

4 TREATMENT PLAN

4.1 AGENT ADMINISTRATION

This is a traditional feasibility study of ^{90}Y TARE, cisplatin, and gemcitabine for unresectable ICC. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for ^{90}Y TARE and cisplatin and gemcitabine are described in Section 9. Appropriate dose modifications for cisplatin and gemcitabine are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Cohorts of at least 2 patients will be treated with ^{90}Y TARE, cisplatin and gemcitabine. The ^{90}Y TARE will be given on day 3 or 4 of cycle 1 and start at 75% (dose level 1) of the dose calculated by the body surface area formula and escalated by 25% per cohort in combination with cisplatin and gemcitabine at the dose levels described in the dose-escalation schedule table below. A TiTE-CRM design will be used to guide dose escalation (see section 11.3 for more details).

Dose-Escalation Schedule					
	(During Cycle 1) Day 3 or 4	Cycle 1 and 2 Days 1 and 8		Cycle 3 + Days 1 and 8	
Dose Level	^{90}Y TARE	Cisplatin	Gemcitabine	Cisplatin	Gemcitabine
0	50%	25 mg/m^2	300 mg/m^2	25 mg/m^2	1000 mg/m^2
1	75%	25 mg/m^2	300 mg/m^2	25 mg/m^2	1000 mg/m^2
2	100%	25 mg/m^2	300 mg/m^2	25 mg/m^2	1000 mg/m^2
3	100%	25 mg/m^2	600 mg/m^2	25 mg/m^2	1000 mg/m^2
4	100%	25 mg/m^2	1000 mg/m^2	25 mg/m^2	1000 mg/m^2

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
^{90}Y TARE	Patient should be on PPI (i.e., Nexium 40 mg)	** in D5	Intra-arterial during hepatic angiography	Days 3 or 4 of cycle 1	21 days (3 weeks)
Cisplatin	Patient should have anti-emetic prophylaxis as indicated in section 7.3	1L NS prehydration followed by 25mg/m^2 in 250 mL NS over 1 hr (+/- 15 minutes)[a]	IV	Days 1 and 8 of each cycle	
Gemcitabine		** in NS given over 30 min (+/- 15 minutes)[a]	IV after 30 min NS infusion following cisplatin	Days 1 and 8 of each cycle	
** Doses as appropriate for assigned dose level. [a]Infusion times may be prolonged due to infusion reactions.					

4.2 ^{90}Y TARE

- The following premedications are suggested:
    - PPI for gastrointestinal prophylaxis prior to ^{90}Y TARE administration. If the patient is on a PPI they can continue their current medication if it is equivalent to Nexium 40 mg daily. If the patient is not on a PPI, they should be started on Nexium 40 mg daily prior to the procedure. Gastrointestinal prophylaxis should continue for 3 months after ^{90}Y TARE.

    - For patients who have had biliary intervention in the past 30 days prior to registration, levaquin 500 mg daily and flagyl 500 mg twice daily starting 3 days before ^{90}Y TARE and continue for 7 days post treatment.

- Selective angiography will be used to deliver the microspheres as selectively as possible. If both lobes are involved then at least two vials will be used to deliver the dose.

- Angiography may be performed via femoral or radial access based on evaluation by the Interventional Radiologist.

- During the initial angiogram, the Interventional Radiologist will determine the hepatic vascular anatomy and coil any vessels that could result in microsphere migration. Tc-99 will be injected and scintography performed to determine lung shunt.

- The Liver CT and/or MRI at registration will be used for planning. The total liver volume, right and left lobes, and tumor volume in each lobe will be contoured. If a more selective delivery will be performed then the appropriate segments and tumor therein will be contoured. The below equation will be used to calculate the dose for each vial to be delivered. The Pre-Implantation Written directive (Appendix B) should be completed and submitted per institutional standards at least one day prior to ^{90}Y TARE. A copy of the directive will also be submitted to the PI.

    $$BSA[m^2] = 0.20247 * height[m]^{0.725} * weight[kg]^{0.425}$$

    $$A[GBq] = BSA - 0.2 + (Tumor\ Volume\ Targeted / Liver\ Volume\ Targeted)$$

- On day 3 or 4 of cycle 1, angiography will be performed and the dose delivered to the appropriate vessel as follows:

    - The Delivery Set will be primed with 5% dextrose for injection.
    - 5% dextrose for injection is injected through the D-line to suspend the SIR-Spheres microspheres in the V-Vial.
    - An aliquot of SIR-Spheres microspheres is loaded into the A-line that leads to the patient.
    - Non-ionic CM is injected through the B-line to flush the SIR-Spheres microspheres into the patient, while at the same time enabling the assessment of microcatheter position, direction and velocity of hepatic arterial blood flow, and confirming the delivery of SIR-Spheres microspheres to the target tissue
    - These steps are repeated until the prescribed activity is delivered to the patient.

- After the delivery of ^{90}Y TARE, radiation safety will perform surveys to ensure no contamination as well as determine the remaining activity in the Delivery Set to calculate the delivered dose. The Post-Implantation Written Directive (Appendix C) should be submitted per institutional

standards no later than 7 days after ^{90}Y TARE. A copy of the directive will also be submitted to the PI.

4.3 DEFINITION OF DOSE-LIMITING TOXICITY

Toxicities will be graded according to the NCI CTCAE scale version 4.0. If multiple toxicities are seen, the presence of DLT should be based on the most severe toxicity grade experienced. DLT will be defined as any of the following events occurring within six weeks from treatment with ^{90}Y TARE.

- Any documented ≥ grade 4 non-hematologic toxicity.
- Any documented grade 3 or 4 neutropenic fever.
- Grade 4 thrombocytopenia or neutropenia > 7 consecutive days.
- Grade 3 non-hematologic toxicity delaying chemotherapy > 21 days.

4.4 DOSE ESCALATION RULES

A CRM design will be used to guide dose escalation of ^{90}Y TARE and gemcitabine due to the long period of evaluation for dose-limiting toxicities. The MTD is defined as the dose with DLT probability of no more than 0.25. By using a weighted likelihood, patients will be enrolled continuously throughout the trial. The following dose escalation rules will be used:

- The first patient will be treated at the second dose level as the first dose is included only as a "fall-back" in the event DLT occurs in the first or second patient.
- The dose assigned to each patient has an estimated DLT rate closest to, but not greater than the target probability.
- Dose escalation is restricted to one level between adjacent patients.
- Escalation from the current dosage is not allowed until both patients assigned to the current dose reach 6 weeks from the start of therapy.
- Discontinue the trial when the probability of DLT at the lowest dose is larger than 25%.
- DLT will be evaluated during the first six weeks from the start of therapy. After a DLT is observed in a cohort, the trial will pause to accrual of the next cohort. The model will be updated to obtain the dose for the next cohort. The updated model, including the proposed dose level for the next cohort, will be sent to the HCC DSMC for approval before restarting accrual. Note that if the first patient in a cohort has a DLT, the 2nd patient will still enroll at the current dose level. The model will be updated after results from both patients have been observed and enrollment will continue after the 2nd patient in the cohort has been followed for 6 weeks.

5 DOSING DELAYS/DOSE MODIFICATIONS

For all study drugs, if a dose is missed or held, the dose will not be made up.

5.1 HEMATOLOGIC

The following dose modifications should be made for febrile neutropenia and blood counts obtained within 2 days prior to each subsequent week. If more than one of these applies, use the most stringent (i.e., the greatest dose reduction).

5.1.1 Cisplatin:

Toxicity	Level	Dose Modification
ANC	< 1000/mm^3	Hold cisplatin Once ANC recovers to ≥ 1.0 K/CUMM , give at full dose at next study treatment day in the current cycle or the first day of the next subsequent cycle.
Platelets	< 75,000/mm^3	Hold cisplatin Once PLT recovers to ≥ 75 K/CUMM, give at full dose at next study treatment day in the current cycle or the first day of the next subsequent cycle.

If cisplatin is held for greater than 21 days then it will be discontinued. There are no dose reductions for Cisplatin.

5.1.2 Gemcitabine:

Dose Level	Gemcitabine
Full Dose	1,000 mg/m^2
-1	750 mg/m^2
-2	500 mg/m^2

For Day 1 and 8 of each cycle, the dose of gemcitabine to be given will depend on the patient's blood counts on that day according to the following table.

ANC (K/CUMM): Day 1	PLT (K/CUMM): Day 1	DOSE MODIFICATION
≥ 1.5 AND	≥ 100	No dose modification
< 1.5 OR	< 100	Hold treatment until recovery of blood counts. If held for > 3 weeks, patient will be removed from study
Day 8	**Day 8**	**DOSE MODIFICATION**
≥1.0AND	≥100	No dose modification
0.75-0.999 AND	≥75	Decrease by 1 dose level. This dose reduction is not permanent.
≥1.0 AND	75 -99.999	Decrease by 1 dose level. This dose reduction is not permanent
0.5-0.749 OR	20-74.999	Omit gemcitabine
<0.5 OR	<20	Omit gemcitabine and reduce by 1 dose level on Day 1 of the next cycle. This dose reduction is permanent

If patients had a non-permanent dose reduction on day 8 and their ANC ≥1.5 K/CUMM and PLT ≥100K/CUMM by day 1 of the next cycle, they will return to full dose (the dose prior to the non-permanent dose reduction).

5.2 NON-HEMATOLOGIC TOXICITY

5.2.1 Cisplatin

Toxicity	Level	Modification
Creatinine Clearance	< 50ml/min	Hold Cisplatin Administer fluids and repeat creatinine as clinically indicated. Administer cisplatin if CrCl ≥ 50 ml/min at full dose at next study treatment day in the current cycle or the first day of the next subsequent cycle. Discontinue if < 50ml/min. after one week
Creatinine Clearance	< 30ml/min	Hold Gemcitabine Administer fluids and repeat creatinine as clinically indicated. Administer gemcitabine if CrCl ≥ 50 ml/min at full dose at next study treatment day in the current cycle or the first day of the next subsequent cycle.
Nausea and/or vomiting	≥ Grade 3, despite maximum antiemetics	Hold cisplatin If improved, cisplatin should be resumed at full dose at next study treatment day in the current cycle or the first day of the next subsequent cycle., if possible If cisplatin is held for ≥ 21 days, discontinue
Neurotoxicity (peripheral)	Grade 1	Full dose
	≥ Grade 2	Hold until improved to grade 1 or better, then resume at full dose at next study treatment day in the current cycle or the first day of the next subsequent cycle. If cisplatin is held for ≥ 21 days, discontinue
Ototoxicity	≥ Grade 3	Discontinue cisplatin

5.2.2 Gemcitabine

General Guidelines:

- Grade 3 or 4 nausea or vomiting only requires dose modifications if it persists > 24 hours despite adequate antiemetic medication.
- There are no dose modifications for alopecia.
- Grade 3 or 4 adverse events not related to treatment such as a thrombosis, pulmonary embolus or non-neutropenic infection do not require dose reductions when treatment is resumed.
- For suspected > grade 2 pneumonitis consult with a medical oncology co- principal investigator.

Toxicity	Grade	Dose Modifications
Other non-hematological toxicities	0-2	Full Dose
	3-4	Hold until resolution to ≤ Grade 2, then decrease by 1 dose level from current dose at next study treatment day in the current cycle or the first day of the next subsequent cycle. If toxicity does not resolve within 3 weeks, discontinue gemcitabine treatment.

6 STUDY ASSESSMENTS

6.1 GUIDELINES FOR STUDY ASSESSMENTS

- Prior to any study specific activities, the patient must be aware of the nature of his/her disease and willingly consent to the study after being informed of study procedures, the experimental therapy, possible alternatives, risks and potential benefits.
- To be completed within 16 days before registration:
    - All blood work, including pregnancy test for WOCBP
    - History and Physical, Vital signs, height/BSA, performance status and Child-Pugh
- To be completed within 28 days prior to registration:
    - CT of chest and pelvis, MRI of abdomen
- Cycle = 21 days
- Chemotherapy should start within 14 days of registration
- To allow for scheduling or holiday issues, patient assessments and drug administration may be done +/- 3 days. Radiographic assessments may be done +/- 7 days.
- Patient assessments must be completed prior to administration of study treatment. Labs obtained within 2 days prior to study treatment will not need to be repeated.

6.2 STUDY CALENDAR

Tests & Observations	Pre-Study	Patient Registration	^{90}Y Eval	Cycle 1			Cycle 2-4		Post cycle 4	Cycle 5-8		Post Cycle 8/ End of Treatment	Follow up[g]	Long Term Follow Up[h]
				Day 1	Day 3 or4	Day 8	Day 1	Day 8		Day 1	Day 8			
Informed Consent	X													
Y90 Precertification	X													
PHYSICAL														
History and Physical Exam	X			X			X			X		X	X	
Vital Signs[b]	X			X		X	X	X		X	X		X	
Height/BSA	X													
Performance Status	X			X			X			X		X	X	
Child's Pugh Classification	X													
Toxicity Assessment[f]				X			X			X		X	X[h]	
Concomitant Medications	X			X		X	X	X		X	X	X		
LABORATORY														
CBC with Differential	X			X	X	X	X	X		X	X			
CMP	X			X	X	X	X	X		X	X	X	X	
Coagulation Panel	X				X									
GGT	X								X			X[l]		
Serum Pregnancy test for WOCBP	X													
SPECIMEN SUBMISSION														
Mutation analysis[a]	X													
X-RAYS AND SCANS														
CT of chest & pelvis	X													
MRI of Abdomen[d]	X								X			X[l]	X	
Hepatic Angiography			X[k]		X									
TREATMENT[e]														
^{90}Y TARE					X									
PPI premedication					X----------								----X	
Gemcitabine				X		X	X	X		X	X			
Cisplatin				X		X	X	X		X	X			
FOLLOW UP														
Vital Status														X

a. If available, tissue from previous biopsy or surgical specimen will be obtained for the mutation analysis. No biopsy will be performed as part of this study. If tissue is not available, the patient is still eligible to participate in the study. Specimen should be submitted within 30 days of registration.
b. Vital Signs include: temperature, blood pressure, heart rate, respiratory rate, and weight
c. CMP is a BMP with the addition of LFTs
d. If contraindication to MRI then 4 phase liver CT will be obtained. Imaging must be completed at MUSC.
e. See section 4 for details regarding treatment administration.
f. Performed according to CTCAE version 4.0.
g. Q 3 months for 2 years after initiation of treatment and then Q 6 months for 4 years until progression. After progression, patients will enter long term follow up
h. After progression, patients will be followed for overall survival and second malignancy until the follow up period is completed.
i. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.
j. Radiographic assessments & GGT should be repeated at the end of treatment visit, unless progression was previously documented.
k. Baseline labs may be used for ^{90}Y evaluation.

7 CONCOMITANT THERAPY

7.1 GENERAL CONSIDERATIONS

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. anti-emetics), with the following exceptions:

- No other investigational therapy may be given to patients.
- No other anticancer agents other than the study medications administered as part of this study protocol must be given to patients. If such agents are required for a patient then the patient must be withdrawn from protocol treatment.
- Growth factors (e.g. G-CSF, G-GM-CSF, erythropoietin, platelets growth factors, etc.) are not to be administered prophylactically but may be prescribed by the treating physician for rescue from severe hematologic events.

7.2 ^{90}Y TARE

The following medications are suggested after ^{90}Y TARE:

- Medrol dose pack for nondiabetics
- Zofran 8 mg to fill if needed
- Percocet 5/325 mg to fill if needed.

7.3 CISPLATIN AND GEMCITABINE

Anti-emetic prophylaxis will be administered as needed as outlined below:

- To reduce the risk of acute emesis, give Zofran 8 mg (IV), aprepitant 125 mg (PO), and Dexamethasone 12 mg (IV) prior to cisplatin.
- An alternative to reduce the risk of acute emesis would be to give Zofran 8 mg, fosaprepitant 150 mg, and Dexamethasone 12 mg (all IV) prior to cisplatin.
- To reduce the risk of delayed emesis give dexamethasone 8 mg daily for days 2-4 and apripetant 80 mg for days 2-3.
- To reduce the risk of delayed emesis if fosaprepitant is given for acute emesis, then give dexamethasone 8 mg once on day 2 and 8 mg bid on days 3 and 4.
- Prehydration, potassium chloride 10 mEq; magnesium sulfate 1 g in NaCl 0.9% 1000 mL infusion

8 PATIENT DISCONTINUATION

Patients may discontinue study treatment at any time. Any patient who discontinues treatment will be asked to return to the study center to undergo end of treatment assessments as outlined within Study Calendar (Section 6). The primary reason for discontinuation should be recorded.
In the absence of treatment delays due to adverse events, treatment may continue for 8 cycles or until one of the following criteria applies:

- Clinical or radiographic disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Estimated lung dose > 30 Gy,
- Uncorrectable extrahepatic deposition on Tc 99 scintography,
- ^{90}Y TARE unable to be given to all disease in one procedure as determined by the Interventional Radiologist or Radiation Oncologist after the initial angiography.
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

8.1 DURATION OF FOLLOW UP

Patients will be followed for progression every 3 months for a maximum of 2 years after initiation of treatment and then every 6 months for 4 years. After progression, patients will be followed for survival and second malignancy.

9 PHARMACEUTICAL INFORMATION

9.1 GEMCITABINE HCL

To supplement the toxicity information contained in this document, see package insert for comprehensive pharmacologic and safety information.

9.1.1 Description

Gemcitabine is an antineoplastic agent that is a cell cycle specific pyrimidine analogue. Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. Gemcitabine is available commercially as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloric salt (expressed as the free base) formulated with mannitol and sodium acetate.

9.1.2 Availability

The commercially available gemcitabine in 200 mg (10 mL vial) or 1 g (50 mL vial) per vial must be prepared for intravenous infusion. Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL. The concentration for 200 mg and 1g vials should be no greater than 40 mg/mL.

9.1.3 Storage and Stability

The lyophilized product should be stored at controlled room temperature (20-25°C or 68-79° F). Once the drug has been reconstituted, it should be stored at controlled room temperature and used within 24 hours. The manufacturer recommends solutions of gemcitabine not be refrigerated as crystallization may occur.

9.1.4 Administration

An appropriate amount of drug will be prepared with normal saline and administered as a 30-minute intravenous infusion.

9.1.5 Toxicity

The major side effects observed with gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to collectively as a flu-like syndrome with fever, headache, rigors, nausea, diarrhea, itchy skin rash, myalgia, and anorexia. Other side effects have included fatigue, peripheral edema, and proteinuria. Less likely side effects include abnormal renal and liver function tests, vomiting, constipation, malaise, and anorexia. Rare side effects include Stevens-Johnson syndrome (severe skin reaction) and shortness of breath, cough, inflammation or scarring of the lung. Rare side effects have also included hemolytic uremic syndrome/renal failure and liver failure have occurred following therapeutic gemcitabine therapy. Cardiac dysfunction (myocardial infarction, congestive heart failure, and atrial fibrillation) have been infrequently reported.

9.2 CISPLATIN

To supplement the toxicity information contained in this document, see package insert for comprehensive pharmacologic and safety information.

9.2.1 Description

Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. Cisplatin is an antineoplastic agent whose mechanism of action appears to be inhibition of the incorporation of DNA precursors, although

protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

9.2.2 Availability

Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH. Cisplatin also is available in vials containing 50mL or 100mL of a 1mg/mL solution.

9.2.3 Storage and Stability

Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

9.2.4 Administration

After administering appropriate antiemetics, cisplatin will be infused intravenously over 1-2 hours along with vigorous hydration.

9.2.5 Toxicity

Human toxicity includes nausea, vomiting, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.

9.3 SIRTEX (YTTRIUM-90 MICROSPHERES)

9.3.1 Description

SIR-Spheres microspheres consist of biocompatible microspheres containing yttrium-90 with a size between 20 and 60 microns in diameter. Yttrium-90 is a high-energy pure beta- emitting isotope with no primary gamma emission.

9.3.2 Availability

SIR-Spheres microspheres are provided in a vial with water for injection. Each vial contains 3GBq of yttrium-90 (at the time of calibration) in a total of 5 cc water for injection. Each vial contains 40 - 80 million microspheres. The vial is shipped within a 6.4mm thick, lead pot. The package consists of a crimp-sealed SIR-Spheres microspheres glass vial within a lead pot, and a package insert within Type A packing bucket.

9.3.3 Storage and Stability

The vial and its contents should be stored inside its transportation container at room temperature (15-25° C, 59-77° F). The useful life of the SIR-Spheres microspheres is 24 hours from the time of calibration.

9.3.4 Dose Preparation (in nuclear pharmacy)

- Unpack SIR-Spheres microspheres, leaving shipping vial in lead pot.
- Place on the bench top in a lead or acrylic shielded box if available.

- Remove the center of aluminum seal from sterile v-vial with forceps, and clean the septum with an alcohol swab.
- Place the v-vial in an empty lead pot (10 cm x 6 cm) for stability and shielding.
- Insert a short 25 gauge needle through the septum of the v- vial until it just pierces the septum to create a vent.
- Remove the SIR-Spheres microspheres shipping vial from the lead pot and shake vigorously to disperse the SIR- Spheres microspheres.
- Using a dose calibrator, determine the activity in the shipping vial and return it to the lead pot.
- Remove partially the aluminum seal of the SIR-Spheres microspheres shipping vial, clean with alcohol swab.
- Insert a 25 gauge needle through the septum of the shipping vial to create a vent, ensuring the needle is well clear of the contents in the shipping vial.
- Use a shielded 5ml syringe with a 21 gauge hypodermic needle at least 50mm long to puncture the septum of the SIR-Spheres microspheres shipping vial, and quickly draw back and forth several times in order to mix the SIR- Spheres microspheres thoroughly.
- Quickly withdraw the pre-calculated patient radiation dose, and transfer into the vented v-vial in the other lead pot. Withdraw the required amount quickly before the contents of the shipping vial start to settle.
- Verify the patient dose in the v-vial by re-measuring the activity in the shipping vial with dose calibrator, and correct, if necessary.
- Put the v vial, containing the confirmed patient dose into the dedicated acrylic shield.

9.3.5 Administration

- The Delivery Set may be primed with either 5% dextrose or sterile water for injection.
- 5% dextrose or sterile water for injection is injected through the D-line to suspend the SIR-Spheres microspheres in the V-Vial.
- An aliquot of SIR-Spheres microspheres is loaded into the A-line that leads to the patient.
- Non-ionic CM is injected through the B-line to flush the SIR-Spheres microspheres into the patient, while at the same time enabling the assessment of microcatheter position, direction and velocity of hepatic arterial blood flow, and confirming the delivery of SIR-Spheres microspheres to the target tissue
- These steps are repeated until the prescribed activity is delivered to the patient.

9.3.6 Toxicity

When the patient is treated with proper technique, without excessive radiation to any organ, the common adverse events after receiving the SIR-Spheres microspheres are fever, transient decrease of hemoglobin, mild to moderate abnormality of liver function tests (mild increase in AST, alkaline phosphatase, bilirubin), abdominal pain, nausea, vomiting, and diarrhea. Severe side effects can include acute pancreatitis, radiation pneumonitis, acute gastritis, radiation hepatitis, and acute cholecystitis.

10 CORRELATIVE STUDIES

If available, tissue from the diagnostic biopsy or previous surgery should be submitted for mutation analysis.

10.1 COLLECTION:

The tissue from the most recent biopsy or surgery should be submitted. Tissue submitted will be formalin-fixed paraffin embedded specimen. The following shall be obtained:

- One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block) or can be the diagnostic slide itself). If a core is sent instead of the block, the region from where the core was punched must be circled by the submitting pathologist.
- A corresponding paraffin-embedded tissue block of the primary tumor (the block must match the H&E being submitted) preferably also containing normal tissue (NOTE: Tissue block that includes normal tissue is encouraged).
- If the institution is not able to release the block, a 5 mm diameter core of tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube (such as an Eppendorf or similar) labeled "tumor" with the surgical pathology number. The punch must come from the same block as the H&E being submitted. Cores should be received for processing within 5 working days of coring.

10.2 HANDLING:

- Storage Conditions: Store at ambient temperature (25C) until ready to ship. Formalin-fixed paraffin-embedded samples should NOT be frozen.
- Ship all samples overnight in a Styrofoam container in order to prevent extreme temperatures during shipping. Please document the storage conditions used and time stored.

10.3 SHIPPING:

Ship the labeled package according to IATA shipping regulations to the following address:

Department of Pathology and Laboratory Medicine
ATTN: Norma Evans/Dr. Schandl (CTO 102254)
165 Ashley Avenue, Suite 309, MSC 908
Charleston, South Carolina 29425
Phone: (843) 792-3500

Samples at MUSC may be delivered to 165 Ashley Ave, Suite 309. Please contact Dr. Schandl 24 hour in advance of drop-off.

10.4 CORRELATIVE STUDY:

The Medical University of South Carolina will perform mutation analysis utilizing the 50-gene RainDance Technologies Thunderbolts Cancer panel.

11 STATISTICAL CONSIDERATION

11.1 PRIMARY ENDPOINT:

Presence or absence of a DLT of ^{90}Y TARE in combination with gemcitabine and cisplatin. All patients who receive any amount of ^{90}Y TARE will be evaluable for toxicity. DLT will be assessed during the first 6 weeks of study treatment and is defined in section 4.3 of this protocol.

11.2 SECONDARY ENDPOINT(S):

- Progression-free survival as defined from the time of enrollment to death or progression utilizing mRECIST criteria.
- Overall survival as defined from time to enrollment to death.
- Percent change in mean volumetric ADC of the index lesion between baseline MRI and at 12 and 24 weeks.
- Classification of diagnostic biopsy or surgical specimen material as proliferative or inflammatory class according to the Illumina TruSight 26 gene test panel.
- GGT obtained from plasma at enrollment and at 12 and 24 weeks.

11.3 STUDY DESIGN

11.3.1 Description of CRM study design

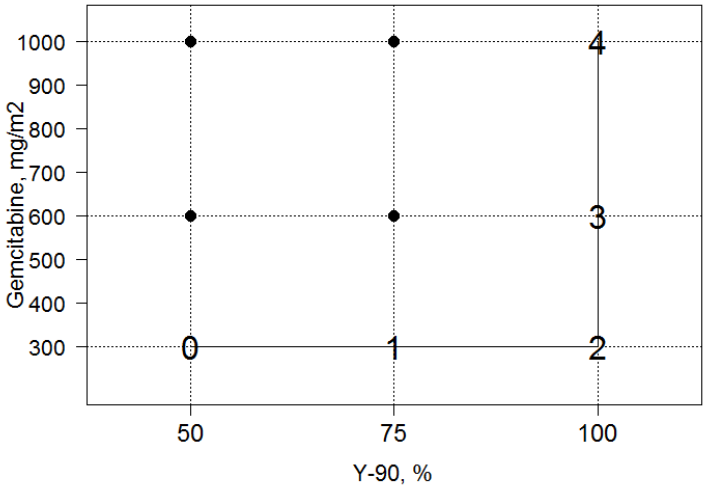
A continual reassessment method (CRM) design will be used to identify the maximum-tolerated dose (MTD) (34). The CRM has been shown to have better properties than the more commonly employed '3+3" design (35). Briefly, it assumes the probability of a DLT at dose *j* is equal to $\pi_j(\alpha) = p_j^{\exp(\alpha)}$ where the p_j values (*j = 0,1,2,3,4* doses which correspond to dose levels listed in dose level table in Section 4.1 and in Figure 11.3.1A) are the "skeleton" for the model. It is an adaptive dose-finding approach where a model-based estimate of the dose is used to determine where the next cohort of patients should be treated based on the accumulated toxicity information from patients already treated on the trial. The R package `dfcrm` (36) will be used to implement the design in the trial. The prior on α has been chosen to be normal with mean 0 and variance 1.34. The dose which has an estimated DLT rate closest to 0.25 will be selected as the MTD.

Our CRM assumes the following characteristics:

- a target DLT rate of 0.25
- cohorts of size 2,
- starts at dose level 1 (75% Y-90; 300 mg/m2 gemcitabine' 25 mg/m2 cisplatin),
- includes restrictions such that
  a. dose levels cannot be skipped (e.g., dose level 2 must be visited before dose level 3 in this case),
  b. dose escalation will not occur immediately following a toxic outcome.
- Our skeleton is $p = \{0.05, 0.15, 0.20, 0.30, 0.40\}$ which is also our prior.
- The trial will terminate after:
  (a) a total of 24 patients have been treated, or
  (b) 10 patients have been treated at a dose which is recommended by the CRM as the dose for the next cohort.
  (c) the estimated DLT rate at the lowest dose level is 0.35 or greater.

Whichever of (a), (b) or (c) occurs first will determine the sample size, which could be as large as 24.

Figure 11.3,1A: Proposed dose levels. The first cohort of 2 patients will be treated at dose level 1 (y-90 at 75%, Gemcitabine at 300 mg/m2. Escalation decisions will be made using the CRM design.



11.3.2 CRM Operating Characteristics

Figure 11.3.2A shows four different true dose-response relationships considered to evaluate the behavior of the proposed CRM, labeled 1 through 4.

- Scenario 1: low toxicity, dose level 4 is optimal
- Scenario 2: moderate toxicity, dose level 2 is optimal
- Scenario 3: synergistic toxicity (ie high toxicity at high dose levels). Optimal dose is 1 or 2.
- Scenario 4: synergistic toxicity with very high toxicity at dose levels 2-4.. Optimal dose is level 0.

Figure 11.3.2A: Four dose-toxicity association scenarios (1 through 4) considered for simulating operating characteristics of CRM design are shown in black. Skeleton is shown in red, and horizontal blue line indicates the target DLT rate (0.25). Scenario numbers (1-4) correspond to the scenarios described in the text and in Table in Section 4.1.

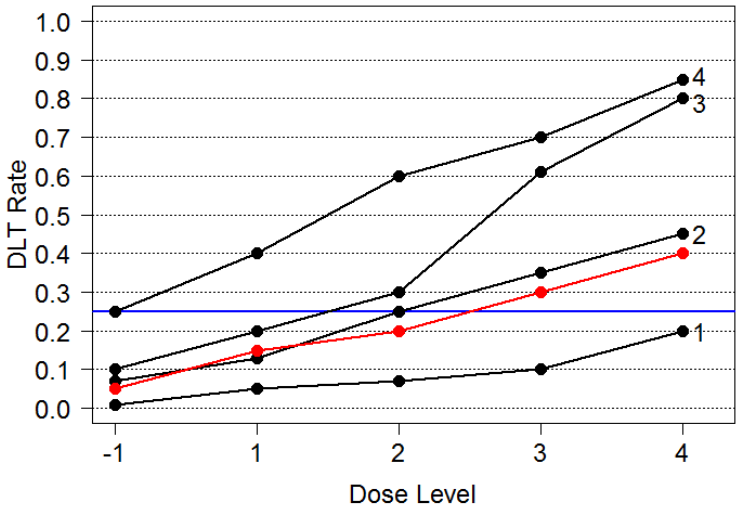


Table 11.3.2A: Operating characteristics of proposed CRM design for **Scenario 1.** Optimal dose is Dose level 4, shown in bold.

	Dose 0	Dose 1	Dose 2	Dose 3	**Dose 4**
True DLT rate	0.01	0.05	0.07	0.10	**0.20**
Probability dose selected	<0.01	<0.01	0.02	0.13	**0.85**
Expected number of pts treated at dose	0.2	2.6	2.7	4.0	**8.7**
Expected number of toxicities observed at dose	<0.01	0.1	0.2	0.4	**1.7**
Expected Sample Size	18.2				
Expected Number of DLTs	2.4				
Expected percent of trials that stop early due to toxicity	<1%				
Expected percent of trials that stop early due to reaching max of 10 at one dose	87%				

Table 11.3.2B: Operating characteristics of proposed CRM design for **Scenario 2.** Optimal dose is Dose level 2, shown in bold.

	Dose 0	Dose 1	**Dose 2**	Dose 3	Dose 4
True DLT rate	0.07	0.13	**0.25**	0.35	0.45
Probability dose selected	0.03	0.24	**0.34**	0.27	0.10
Expected number of pts treated at dose	1.3	5.5	**6.0**	4.6	2.2
Expected number of toxicities observed at dose	0.1	0.7	**1.5**	1.6	1.0
Expected Sample Size	19.7				
Expected Number of DLTs	4.8				
Expected percent of trials that stop early due to toxicity	2%				
Expected percent of trials that stop early due to reaching max of 10 at one dose	72%				

Table 11.3.2C: Operating characteristics of proposed CRM design for **Scenario 3.** Optimal doses are dose levels 1 or 2, shown in bold.

	Dose 0	**Dose 1**	**Dose 2**	Dose 3	Dose 4
True DLT rate	0.10	**0.20**	**0.30**	0.61	0.80
Probability dose selected	0.10	**0.48**	**0.33**	0.03	<0.01
Expected number of pts treated at dose	2.5	**7.5**	**5.7**	2.4	0.2
Expected number of toxicities observed at dose	0.3	**1.5**	**1.7**	1.4	0.2
Expected Sample Size	18.4				
Expected Number of DLTs	5.1				
Expected percent of trials that stop early due to toxicity	6%				
Expected percent of trials that stop early due to reaching max of 10 at one dose	78%				

Table 11.3.2D: Operating characteristics of proposed CRM design for **Scenario 4.** Optimal dose is dose level 1, shown in bold.

	Dose 0	Dose 1	Dose 2	Dose 3	Dose 4
True DLT rate	**0.25**	0.40	0.60	0.70	0.85
Probability dose selected	**0.36**	0.21	<0.01	<0.001	<0.001
Expected number of pts treated at dose	**5.5**	5.1	1.5	0.3	<0.1
Expected number of toxicities observed at dose	**1.4**	2.1	0.9	0.2	<0.1
Expected Sample Size	12.4				
Expected Number of DLTs	4.5				
Expected percent of trials that stop early due to toxicity	43%				
Expected percent of trials that stop early due to reaching max of 10 at one dose	53%				

11.3.3 Phase I Analysis Plans

The CRM design will guide us to a dose to select for expansion in the Phase II portion of the study. For each dose level, the DLT rate with a 95% confidence interval will be reported.

11.4 SAMPLE SIZE/ACCRUAL RATE

HCC is a hepatobiliary referral center and treats 10 patients with ICC per year. All patients are discussed at our multi-disciplinary tumor board where they are considered for eligibility for clinical trials with a dedicated gastrointestinal research coordinator. We expect to enroll up to 24 patients. Based on historic numbers (10 eligible patients per year) and competing protocols (currently none), we estimate an accrual rate of 1 patient every two months. At this rate we would expect to meet the overall accrual goals of the trial within 3 to4 years. A Patient Decline Questionnaire will be utilized to identify barriers to enrollment with the expectation of amending the protocol as needed to address accrual deterrents.

11.5 STRATIFICATION FACTORS

There will be no stratification factors.

11.6 ANALYSIS OF SECONDARY ENDPOINTS

Progression-free survival and overall survival will be determine by Kaplan-Meier analysis and defined from the time of enrollment to death or progression utilizing mRECIST criteria. Cox regression will be used to determine if percent change in mean volumetric ADC of the index lesion between baseline MR and at 12 and 24 weeks are related to overall survival.

The log rank test will be used to compare the overall survival for the inflammatory and proliferative classes.

Cox regression will be used to determine if baseline GGT or change in GGT at 12 and 24 weeks are related to overall survival.

12 MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated after four cycles. In addition to a baseline scan, confirmatory scans will also be obtained after 4 cycles following initial documentation of an objective response.

12.1 ANTITUMOR EFFECT – SOLID TUMORS

Response and progression will be evaluated in this study using the modified mRECIST criteria endorsed by the American Association for the Study of Liver Disease (AASLD) (37) Changes in only the largest diameter (unidimensional measurement) of the tumor enhancing component are used in the mRECIST criteria.

12.2 DEFINITIONS

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ^{90}Y TARE

Evaluable for objective response. All patients will have measurable disease present at baseline. If they have received at least one cycle of therapy and have had their disease re-evaluated, they will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

12.3 DISEASE PARAMETERS

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.4 METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

12.5 RESPONSE CRITERIA

Disease response will be documented using mRECIST.

12.5.1 Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameter (LD) of target lesion enhancing component, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target viable lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

12.5.2 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.5.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

12.6 DURATION OF RESPONSE

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

12.7 PROGRESSION-FREE SURVIVAL

PFS is defined as the duration of time from start of treatment to time of progression.

13 DATA REPORTING/REGULATORY REQUIREMENTS

Electronic and hard copy CRF's will be provided for the recording of data. With the exception of hard copy case report forms utilized for expedited reporting requirements, such as the reporting of SAE's, the remainder of patient data will be collected and submitted via electronic CRFs. All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed.

Electronic data for on study and follow-up patient data is submitted via the electronic system called REDCap. REDCap is managed from MUSC as a consortium partner under their CTSA. REDCap is a secure, Web-based application designed to capture and manage research study data.

The system has been reviewed for 21CFR Part 11 compliance and has been deemed "21CFR 11 Capable." Users of the REDCap system are limited to members of the IRB approved research team who are delegated data management responsibilities, typically the study coordinator and data manager. A report with compliance information is available upon request.

14 ADVERSE EVENTS: REPORTING REQUIREMENTS

The descriptions and grading scales found in the revised NCI CTCAE version 4.0will be utilized for AE reporting. In addition, SAEs have special reporting requirements. AE and SAE criteria and reporting requirements are outlined in this section. For both serious and non-serious adverse events, the investigator must determine the severity of the event, "expectedness" of the event, and the relationship of the event to study treatment administration.

The study period during which all AEs and SAEs must be reported begins after initiation of study treatment and ends at end of cycle 8 or end of treatment. After this period, investigators should only report AEs that are attributed to ^{90}Y TARE. SAEs should be monitored until they are resolved or are clearly determined to be due to the patient's stable or chronic condition or intercurrent illness(es)

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

14.1 PURPOSE

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner during a trial. Additionally, certain AEs must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe routine and expedited adverse event reporting for this protocol.

Throughout the study, the Investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

14.2 DEFINITION OF ADVERSE EVENT

An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subjects All toxicities, serious and non-serious, $\geq$ grade 2 that were not present at baseline will be reported in the REDCap AE database. Only clinically significant grade 3 or 4 abnormal lab values that were not noted during the screening phase should be recorded; however, any clinical consequences of the abnormality, regardless of grade, should be reported as AEs.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency, duration or severity, or a change in the quality, of the disease or condition. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Progression of cancer also will not be considered an AE.

14.3 DEFINITION OF SERIOUS ADVERSE EVENT

An SAE is defined as any event that results in one of the following outcomes:

- death
- life threatening (places the subject at immediate risk of death)
- inpatient hospitalization or prolongation of existing hospitalization. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes
- disability or permanent damage. Report is the event resulted in a substantial disruption of a person's ability to conduct normal life functions.
- congenital anomaly/birth defect.
- requires intervention to prevent permanent impairment or damage
- important medical important events. Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

14.4 SERIOUS ADVERSE EVENT REPORTING

The Investigator must report all SAEs to the SIS Unit **within 24 hours of first becoming aware of the event**. This report will be accomplished by completing the 102254 SAE form in REDCap (redcap.musc.edu). Any missing or additional relevant information concerning the SAE should be provided in a written follow-up report. SAE reporting for this study will follow FDA guidelines for Medical Device Reporting.

All SAEs should be monitored until they are resolved or are clearly determined to be due to the patient's stable or chronic condition or intercurrent illness(es).

14.5 DEFINITION OF SEVERITY

Adverse events will be graded according to the revised NCI Common Toxicity Criteria. If toxicities are not defined by the NCI CTCAE v. 4.0, the intensity of each adverse event should be graded as either Mild (grade 1), Moderate (grade 2), Severe (grade 3), or Life-threatening (grade 4) by the Investigator.

GRADE 1	MILD: Sign or symptom noticeable, but does not interfere with normal daily activities.
GRADE 2	MODERATE: Sign or symptom sufficient to interfere with normal daily activities.
GRADE 3	SEVERE: Sign or symptom is incapacitating, with inability to perform daily activities.
GRADE 4	LIFE-THREATENING: sign or symptom poses immediate risk of death to this patient.

14.6 ATTRIBUTION OF THE AE

Definite:	AE is clearly related in time and a direct association can be demonstrated to the study intervention
Possible:	AE may be reasonably related in time and the AE can be explained equally well by causes other than the study intervention
Unrelated:	AE is clearly not related to intervention and can be fully explained by another cause. This other cause should be provided.

14.7 ADVERSE EVENT "EXPECTEDNESS"

Expected adverse events are those adverse events that are listed or characterized in the Package Insert.

Unexpected adverse events are those not listed in the package Insert. This includes adverse events for which the specificity or severity is not consistent with the description in the Package Insert. (For example, under this definition, hepatic necrosis would be unexpected if the Package Insert only referred to elevated hepatic enzymes or hepatitis.)

15 MONITORING

The SIS Unit will be responsible for the monitoring of study patient data and records. All patients' eligibility criteria will be audited by the SIS Unit prior to patient registration. During the course of the study, each site will be selected for an audit approximately twice a year. The number of cases reviewed will be commensurate with the site's rate of enrollment.

15.1 PROTOCOL DEVIATIONS

A **Protocol Deviation** is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval. Any protocol deviation will be reported by the site within 10 days of notification.

15.2 SAFETY REPORTING

All toxicities, serious and non-serious, that represent a new side effect or toxicity greater than baseline will be reported by the sub-site via the REDCap electronic case report form. In addition, SAEs have special reporting requirements. SAE criteria and reporting requirements are outlined in section 14.

15.3 DATA SAFETY MONITORING COMMITTEE

The HCC DSMC will have oversight of the protocol. The HCC DSMC will meet, at a minimum, on a semi-annual basis to discuss this investigator-initiated trial. Also, this study will be audited by the HCC DSMC auditor) approximately two times per year.

In addition, all protocol deviations and SAEs as defined above will be reviewed by the HCC DSMC at monthly meetings. As new protocol deviations or serious adverse events are reported to the SIS Unit, the SIS Unit will review these reports for form completion and follow up if more information is warranted. The SIS Unit will forward the event report to the HCC DSMC so that the information can be reviewed at the next available HCC DSMC meeting. During the HCC DSMC review, the HCC DSMC can make recommendations for any further study action.

16 APPENDICES

APPENDIX A
National Cancer Institute Common Toxicity Criteria, Version 4.0

HTTP://WWW.EORTC.BE/SERVICES/DOC/CTC/CTCAE_4.03_2010-06-14_QUICKREFERENCE_5X7.PDF

APPENDIX B

Pre-implantation Written Directive

See next page

PRE-IMPLANTATION WRITTEN DIRECTIVE

Patient Name: *Last, First* **Study ID** **Treatment Site:** Liver

Scheduled Treatment Time:

Eq. 1 Mass of Target Liver (Kg)= (Density * Volume -> 1.03gm/cc * 1kg/1000gm*Volume (cc))

Eq .2: Estimated Dose to Perfuse Liver Tissue (Gy)= 50*[Injected Activity (GBq) * [1-LSF]*[1-R]
Mass of Target Liver, Kg

Eq .3: Est. Dose to Lung(Gy)= 50*[Injected Activity (GBq) * [LSF]*[1-R]

Maximum acceptable dose to lungs: 30Gy (from all administrations)

Right		**Left**	
Radiopharmaceutical:	SIR-Tex Y-90	**Radiopharmaceutical:**	SIR-Tex Y-90
Target Tissue/Tx. Site (Rt., Lt. Lobe, or Whole):		Target Tissue/Tx. Site (Rt., Lt. Lobe, or Whole):	
% Lung Shunting (LSF):		% Lung Shunting (LSF):	
Desired Activity:	mCi	**Desired Activity:**	mCi
Accep. Act. Range(+ 10%):	to	Accep. Act. Range(+ 10%):	to
Volume of target/infused liver:	cc	**Volume of target/infused liver:**	cc
Mass of target liver :	Kg	**Mass of target liver :**	Kg
Est. dose to be del. to perfused liver*:	Gy	**Est. dose to be del. to perfused liver*:**	Gy
Est. dose to be delivered to lungs:**	Gy	**Est. dose to be delivered to lungs**:**	Gy

*Eq. 3 Assumed no residual **Eq. 2 Assumed no residual

Est. Total dose to be delivered to lungs(Gy): 0.0

Number of Vials			
dose	Right		mCi
	Left		mCi

Radiation Oncologist:

Radiation Oncology Physicist:

Radiopharmacy Meas. Activity: Right mCi
Left mCi

Time of measurement:

Nuclear Pharmacist		
Desired Activity is within acceptable range	Yes	No
Note:		
Radiation Oncologist:	Radiation Oncology Physicist:	

APPENDIX C

Post-Implantation Written Directive

See next page

POST-IMPLANTATION WRITTEN DIRECTIVE

Patient Name: *Last, First* | **Study ID** | **Treatment Site:** Liver

Scheduled Treatment Time:

Prescribed Activity Left: _____ mCi GBq

Prescribed Activity Right: _____ mCi GBq

Eq. 1 Mass of Target Liver (Kg)= (Density * Volume -> 1.03gm/cc * 1kg/1000gm*Volume (cc))

Eq .2: Estimated Dose to Perfuse Liver Tissue (Gy)= $\frac{50*[\text{Injected Activity (GBq)} * [1-\text{LSF}]*[1-\text{R}]}{\text{Mass of Target Liver, Kg}}$

Eq .3: Est. Dose to Lung(Gy)= 50*[Injected Activity (GBq) * [LSF]*[1-R]

Maximum acceptable dose to lungs: 30Gy (from all administrations)

Estimated % Delivered(Left):
Estimated % Delivered(Right):
Delivered Activity(Left) : mCi GBq
Delivered Activity(Right) : mCi GBq

Total Delivered Activity: mCi GBq

Estimated dose delivered to perfused Left liver: Gy Eq 2
Estimated dose delivered to perfused Right liver: Gy Eq 2
Estimated dose delivered to lung: Gy Eq 3

Pt. Identification: (@ least 2 criteria) YES NO

Dose **was not** stopped due to decreased flow/stasis/other clinical factors: YES NO

Injected Act. is within acceptable range YES NO

Highest Exposure Rate Measured by RSO: mR/hr at 1meter from patient surface

Note:

Radiation Oncologist:	Radiation Oncology Physicist:

APPENDIX D

Patient Decline Questionnaire

See next page

Thank you for thinking about participating in the Yttrium 90 intrahepatic cholangiocarcinoma trial. It would be helpful if you could tell us the reasons you have decided not to participate. This will help us to develop trials that future patients might find more agreeable to join. Your response will be completely anonymous.

Please complete the following questionnaire and either leave it at the clinic front desk, or drop it in the mail.

Date: _____

I have decided not to sign the informed consent document.

The reasons for my decision include the following *(check all that apply)*:

- ☐ I decided against being in any clinical trial
- ☐ I had concerns about fitting this into my life
  - ○ The trial involves too many extra clinic visits
  - ○ The trial is too far from home
  - ○ I want to be treated by local doctor
  - ○ I have family and/or job issues
- ☐ I had concerns about the procedures I would have to do
  - ○ Too many MRIs
- ☐ I had concerns about the treatment I would receive
  - ○ Yttrium 90 microspheres
  - ○ Gemcitabine and cisplatin chemotherapy
  - ○ Frequency of when I would be getting treatment
- ☐ I had concerns about my insurance and/or financial concerns
- ☐ Other *(please specify):*_____

_____

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APPENDIX E

Performance Status Scale

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

APPENDIX F

ASSESSMENT OF THE CHILDS-PUGH CLASSIFICATION

Clinical and Biochemical Measurements		Points Scored for Increasing Abnormality		
	Check box below Refer to points scored columns on right	**1**	**2**	**3**
Hepatic encephalopathy (grade)*	☐1 ☐2 ☐3	**None**	**1 and 2**	**3 and 4**
Date hepatic encephalopathy was assessed: _____				
Ascites	☐1 ☐2 ☐3	**Absent**	**Mild**	**Moderate**
Date ascites was assessed: _____				
Total bilirubin (mg/dl)	☐1 ☐2 ☐3	**< 2.0**	**2.0 - 3.0**	**> 3.0**
Date Total bilirubin was assessed: _____				
Serum albumin (g/dl)	☐1 ☐2 ☐3	**> 3.5**	**2.8 - 3.5**	**< 2.8**
Date Serum Albumin was assessed: _____				
Prothrombin time (sec. prolonged) or Prothrombin time INR**	☐1 ☐2 ☐3	**< 4 or < 1.7**	**4 - 6 or 1.7 - 2.3**	**> 6 or >2.3**
Date Prothrombin time or Prothrombin time INR was assessed: _____				

TOTAL POINTS: _____
CHILD-PUGH GRADE: _____

Grade A (well-compensated disease) = Total score 5-6
Grade B (significant functional compromise) = Total score 7-9
Grade C (decompensated disease) = Total score 10-15

Investigator Signature: _____ Date: _____

APPENDIX G

NEW YORK HEART ASSOCIATION CLASS

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to Work
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

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