The Theranostic Approach Towards Personalized Medicine Using Low Dose Y90 Microspheres for Radioembolization Therapeutic Planning (A Phase 2 Study)

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EMORY
WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

Winship Protocol #: *RAD4784*

TITLE: The Theranostic Approach Towards Personalized Medicine Using Low Dose Y90 Microspheres for Radioembolization Therapeutic Planning (A Phase 2 Study)

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[redacted]

A study can have only one Principal Investigator. The Principal Investigator is responsible for all study conduct.

The Principal Investigator and all physicians responsible for patient care must have a current FDA Form 1572, Financial Disclosure Form (if IND study), CV & Medical license on file, and completed eCOI and Human Subjects training.

[redacted]

Study Coordinator:

[redacted]

Responsible Research Nurse:

[redacted]

Responsible Data Manager/Statistician#2:

[redacted]

Supplied Agent: Sirsphere (Yttrium-90 Resin Microsphere), SIRTEX Medical LTD, [redacted]

The product is FDA approved and does not required IND per 21 CFR 312.2(b).

Protocol Type / Version # / Version Date: *[Original / Version #2 / August 22, 2019]*

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1 PROTOCOL SUMMARY

1.1 Synopsis

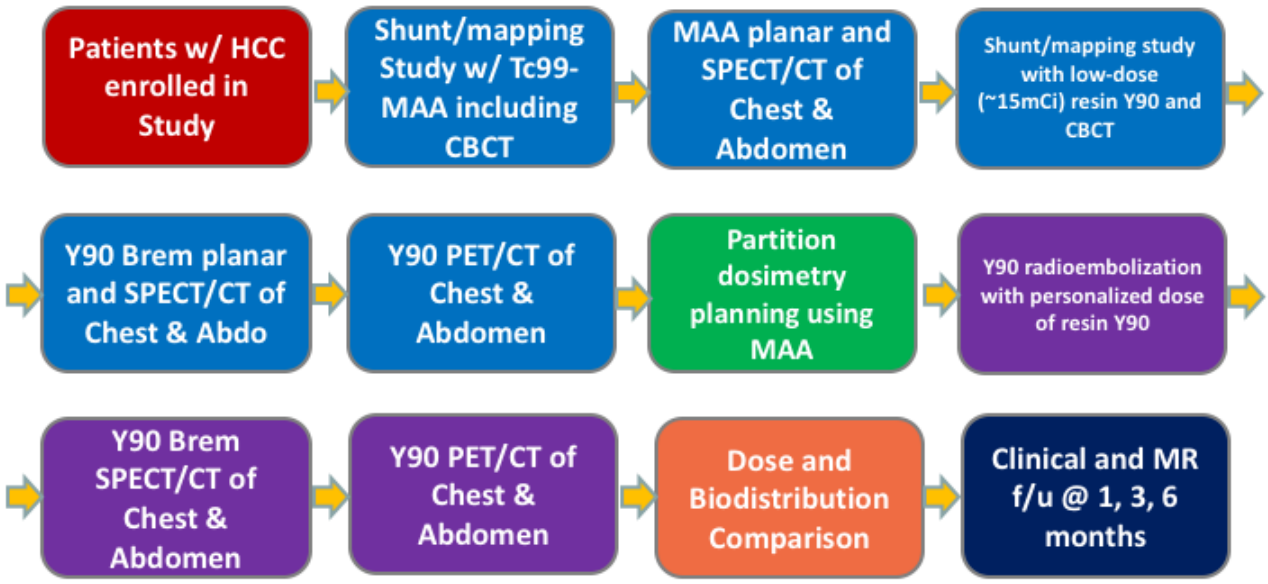
Title:	The Theranostic Approach Towards Personalized Medicine Using Low Dose Y90 Microspheres for Radioembolization Therapeutic Planning (A Phase 2 Study)
Study Description:	Hepatocellular carcinoma (HCC) is the second deadliest cancer globally, with a 5-year survival of 18% in the and less than 20% of patients eligible for curative surgical treatment. Although Yttrium-90 (Y90) radioembolization (RE) is an established therapy in patients

	with unresectable HCC, it has variable response due to many internal and external factors, including tumor histology and vascularity. A critical factor predicting tumor response (TR) is delivery of tumoricidal dose to targeted lesions. Optimizing individualized Y90 dosimetry will likely improve targeted TR and survival, while minimizing lung and liver toxicity. Technetium-99m macroaggregated albumin (^{99m}Tc-MAA) is currently used as the primary radiotracer for shunt studies prior to Y90 RE. However, ^{99m}Tc-MAA falls short in accurately predicting Y90 biodistribution in the liver and lung after RE. By evaluating the safety and efficacy of low dose Y90-microspheres as the radiotracer for pre-treatment shunt study, our goal is to address an unmet public health need by improving TR post-Y90 therapy through prospective personalized dosimetry. **We hypothesize that using low dose Y90 microspheres as the treatment planning radiotracer will allow accurate prediction of therapeutic Y90 liver biodistribution, which will enable us to perform prospective personalized dosimetry for every individual patient.** The results of this study will determine the safety and efficacy of using low dose Y90 as a direct surrogate for treatment planning to ensure delivering cytotoxic Y90 dose to the targeted tumor(s), while concomitantly minimizing liver and lung toxicity with more accurate prediction of therapeutic Y90 biodistribution. **Our long-term objective is to increase the likelihood of objective tumor response, prolonged progression-free survival (PFS) and overall survival (OS) in patients with HCC treated with Y90 RE.**
Objectives:	Primary Objective: **Compare the safety and accuracy/efficacy of low dose Y90 resin microspheres and MAA in predicting the actual dose delivered to the tumor, liver, and lung after Y90 therapy.** Secondary Objectives: *1.* **Optimize low dose Y90 techniques in predicting TNR and LSF.** *2.* **Identify tumor dose response thresholds (TDRT) and tumor dose distribution in patients with HCC treated with Y90 resin microspheres.**
Endpoints:	Primary Endpoint: The lung shunt fraction (LSF) and tumor to normal liver activity ration (TNR). Secondary Endpoints: 1. Monitoring all grades of Y90 related toxicity

	2. Tumor response evaluation at 1, 3 and 6 months and determination TDRT
Study Population:	N=30 patients with hepatocellular carcinoma (HCC), male or female, =>18 years of age, all ethnicities, ECOG <2, and generally local patients referred to Winship.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	All patients will be recruited at Emory Interventional Radiology Clinics after they have been discussed and referred through multidisciplinary liver tumor boards. Only patients that are found to be ideal candidates for Y90 radioembolization at tumor boards will be considered for recruitement. Emory University Hospital and Emory University Hospital Midtown will be the clinical sites to perform the study.
Description of Study Intervention:	In this study, patients with HCC who are found to be ideal candidates for HCC and who would fit our inclusion criteria, described below, will be recruited. Patients will undergo standard of care mapping study with ^{99}TC-MAA to plan for Y90 radioembolization therapy. The additional, non-standard of care, intervention will be to do a second mapping study using low-dose Y90 (15 mCi) before the therapeutic Y90 radioembolization. The distribution of MAA in terms of lung shunt fraction (LSF) and tumor to normal liver activity ration (TNR) will be compared to that of low-dose Y90. The treatment planning will be performed using standard of care MAA biodistribution using partition dosimetry model. After administration of therapeutic Y90 dose, the actual dose delivered to tumor, non-tumoral liver (NTL) and lungs will be compared to the dose predicted by MAA and low-dose Y90. The patients will be the followed-up clinically and with imaging at 1, 3 and 6 months to determine tumor response, potential treatment related toxicity and to determine TDRT.
Study Duration:	24 months
Participant Duration:	6 months

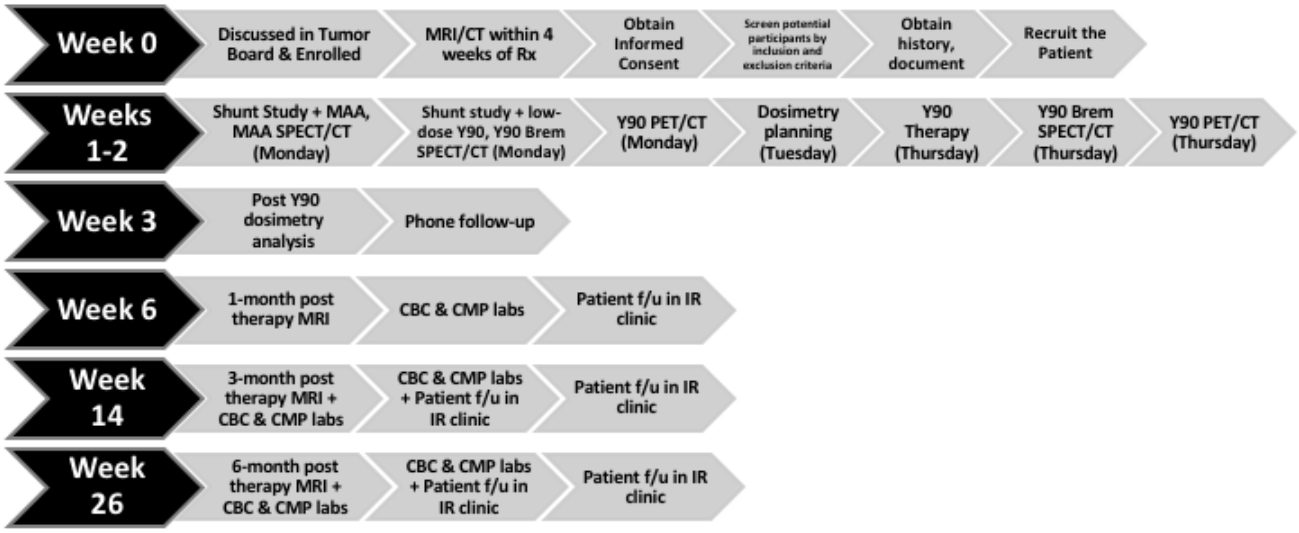
1.2 Schema

Overall Study Flow Chart



1.3 Schedule of Activities (SoA)

Study Flow Chart for Individual Patients



Estimated Timeline for Weeks 1-2 (Mapping and Treatment Week)

<u>Monday:</u>

<u>7:30 AM-9:30 AM:</u> 1st Angiographic study for mapping and MAA delivery

10:00 AM-11:00 AM: MAA SPECT/CT (Patient will go to nuclear medicine with radial/femoral arterial access sheath in place)

11:30 AM-1:00 PM: 2nd Angiographic study for low-dose Y90 delivery (After the procedure, patient's femoral sheath will be removed and hemostasis will be achieved with manual compression or closure device. If procedure performed via radial access, which is more commonly performed currently at Emory, the radial sheath will stay in and removed according to IR protocol after Y90 SPECT/CT.)

2:00 PM-3:00 PM: Y90 Bremsstrahlung SPECT/CT

3:00 PM-3:30 PM: Removal of the radial sheath at IR post procedural area and discharge.

4:30-5:30 PM: Y90 PET/CT.

Patient is free to go home after this.

Thursday:

11:00 AM-12:30 PM: 3rd angiographic study to deliver therapeutic dose of Y90.

1:00 PM-2:00 PM: Y90 Bremsstrahlung SPECT/CT (After the procedure, patient's femoral sheath will be removed and hemostasis will be achieved with manual compression or closure device. If procedure performed via radial access, which is more commonly performed currently at Emory, the radial sheath will stay in and removed according to IR protocol after Y90 SPECT/CT.)
3:00 PM-3:30 PM: Removal of the radial sheath at IR post procedural area and discharge.

4:30-5:30 PM: Y90 PET/CT.

Patient is free to go home after this.

Study Procedures	Screening Visit **Week 0**	Therapy planning/mapping **Week 1-2**	Y90 sirsphere treatment **Week 1-2**	1 week post procedure **Week 6**	1 month post procedure **Week 6**	3 months post-procedure **Week 14**	6 months post-procedure **Week 26**
Informed consent	X						
Entry Criteria	X						
Demographics	X						
Medical/surgical Hx	X						
Blood sampling	X				X	X	X
Collect list of medications	X						
Vital signs	X						
Physical exam	X						
Phone follow-up by Dr. Kokabi or Research Nurse				X			
MRI W & WO contrast	X				X	X	X
Conventional MAA angiography		X					
Low doseY90 shunt study angiography		X					
SPECT/CT		X	X				
PET/CT		X	X				
Y90 Treatment			X				
Post Procedure Clinic follow up					X	X	X

2. INTRODUCTION

2.1 Study Rationale

Less than 20% of patients with HCC are eligible for curative surgical resection in the United States, with a 5-year survival of 18%[1]. Y90 therapy has demonstrated efficacy in HCC as both palliative therapy and bridge to “definitive therapy” such as transplantation by providing

locoregional disease control[2]. However, multiple factors affect objective TR to Y90 RE, including appropriate cytotoxic dose delivery to the targeted tumors[3, 4].
A direct dose-response relationship exists between delivered Y90 dose to the tumoral and normal non-tumoral liver (NTL), TR and hepatic toxicity[5-12]. Improvements in PFS and OS have been shown to occur in patients achieving objective TR across the majority of primary and metastatic liver tumors treated with Y90 RE[5, 6, 8, 9, 13-24]. These findings imply that the determination of tumor-specific dose response thresholds and optimization of tumor dose delivery while minimizing NTL dose will likely further improve post Y90 RE outcome. However, reported TDR thresholds predicting objective TR vary widely, not only by malignancy type and grade, reflecting differential tumoral radiosensitivity, but also within the same tumor types and under similar conditions[17-19, 25]. Additionally, reported TDR thresholds in HCC for resin and glass microspheres are significantly different[7, 26]. Furthermore, both glass and resin Y90 microspheres demonstrate heterogeneity in distribution and absorbed radiation when delivered intra-arterially[27, 28]. Autoradiographic and pathologic analysis of patients with HCC treated with Y90 demonstrated a tendency for Y90 RE material to localize along the tumor periphery[27, 28]. Given that Y90 is a pure beta emitter with short tissue penetration of 2.5mm, absorbed radiation dose at the center of large tumors can be as low as 20 Gy, while the periphery of the tumor can receive >230 Gy[27-29]. Numerous factors are presumably responsible for such phenomenon, including tumor vascular density, flow dynamics, number of particles administered and clustering of particles. Of note, distribution of the particles and absorbed radiation is more homogenous in NTL compared to tumors, likely due to organized vasculature[27-29].

The above observations suggest that the use of **mean absorbed dose** for the entirety of the tumor is inaccurate for determining TDR because a single small area of microsphere concentration may spuriously suggest that a tumoricidal dose has been achieved. We believe that wide ranges in previously reported TDR thresholds are largely explainable by disparities in dosimetry methodology used by different investigators, the inadequacy of currently employed Y90 RE dosimetric techniques in addressing the complex interactions between the tumor microvasculature, RE devices (glass vs. resin) and resulting radioactive microsphere biodistribution[7, 30]. Other factors including the indirect and continuous Bremsstrahlung radiation spectrum detected on SPECT and alteration in flow biomechanics by surrogate injection may play secondary roles[7].

Manufacturer recommended Y90 RE dosimetry models include empiric (set dose of radiation delivered to liver lobe regardless of tumor type) and a variation of the body surface area method which can additionally factor in tumor volume as determined by cross-sectional imaging[31, 32]. Not only do these methods rely on variables that poorly correlate to absorbed dose prediction and Y90 microsphere biodistribution, they also fail to consider the highly unique tumor micro- and macro-environment. To date, the partition model is the most studied personalized dosimetry model, requiring the determination of MAA uptake TNR during the shunt study using

SPECT/CT[33]. In the partition model, MAA is assumed to mirror Y90 biodistribution and to distribute uniformly within the liver tumor and NTL, but at different concentrations. Such assumptions facilitate calculation of Y90 doses separately for the tumor and NTL which can be used to plan treatments based on dose limits that are thought to minimize pulmonary and hepatic toxicities[33, 34].

While the assumption of MAA mirroring the Y90 microsphere biodistribution has long been suspected to be inaccurate, only recently has its impact on dosimetry been quantified, with especially compelling data sourced from the current reference standard post-Y90 PET/CT, comparing the actual Y90 absorbed dose to that estimated from the MAA[19, 25, 27]. MAA has been shown to be an inaccurate estimator of LSF and Y90 biodistribution in the liver due to several factors, including size discrepancy between MAA and Y90 microspheres, as well as free pertechnetate overestimating LSF[35-37]. MAA consistently overpredicts LSF, sometimes by greater than 100%, and has a poor linear correlation with directly measured LSF using Y90 PET (correlation coefficient: 0.682)[25]. Conversely, MAA underpredicts TNR compared to that obtained on post Y90 SPECT and PET, with a wide range of linear coefficient ranging from 0.7-0.9[8, 25]. Furthermore, retrospective direct Y90 tumor dose measurement using PET and SPECT after Y90 therapy, while resource intensive, has limited clinical benefit, since patients are rarely retreated if "inadequate" dose is delivered to tumor[8, 25]. **Hence, there is a critical need to ensure the desired dose is estimated accurately in a prospective fashion prior to administration of the therapeutic Y90.**

These problems can be overcome by using a radioactive tracer in pre-treatment planning that is bioidentical to Y90 microspheres, which is the principle behind shunt study and treatment with Holmium-166 microspheres (^{166}Ho)[38]. Currently, ^{166}Ho is not available in the United States, and low-dose Y90 microspheres are the most readily available direct surrogate to predict LSF and tumor dose. Similar to the use of low-dose ^{166}Ho for treatment planning, a prospective personalized dosimetry method using direct yet non-toxic surrogate for therapeutic Y90 microspheres is necessary to further optimize Y90 dosimetry in a clinically pertinent manner. We believe that such efforts will not only standardize Y90 RE methodology and improve post Y90 RE outcomes under currently recommended indications but will also better allow accurate study of further indications. Additionally, LSF is a major determinant in the calculation of a safe Y90 dose as LSF > 20% is a relative contraindication to Y90 RE. Hence, it is possible that patients with inaccurately high LSF's estimated by MAA may receive lower suboptimal Y90 therapeutic doses or are entirely excluded from treatment, thus adversely impacting post-Y90 outcomes.

In summary, there is growing evidence that factoring individual patient characteristics into Y90 treatment planning are likely to significantly impact both TR and treatment tolerability. To this end, the partition model, while more resource intensive, has made great strides towards treatment individualization. However, the use of MAA in predicting post Y90 RE absorbed dose and

biodistribution is flawed and inaccurate, leading to suboptimal dose delivery, unnecessary hepatotoxicity and poor outcomes. **Therefore, we propose low-dose Y90 microspheres for therapy planning, as an alternative to MAA, to be a bioidentical therapeutic Y90 surrogate marker to better predict and thus achieve optimal therapeutic dosing.** Our long-term goal is to improve TR, PFS, and OS while reducing potential associated toxicities in patients treated with Y90 RE.

2.2 Background

2.2.1 Clinical experience

A) A 68-year-old male with a solitary caudate lobe HCC measuring 6.2 cm with macrovascular invasion was referred to Y90 RE by a multidisciplinary tumor board. The patient's baseline CT and MRI findings were concerning for high LSF due to opacification of hepatic veins and IVC on arterial phase of the scans. His lung shunt fraction using MAA was 44%. He was brought back to the IR and a shunt study using low-dose (**9.1 mci**) resin microspheres was performed. The planar bremsstrahlung LSF was measured at 29% (**Figure 1A**). The therapeutic Y90 dose was modified to ensure lung dose of <30Gy from both low and therapeutic dose Y90 RE's. The patient was then successfully treated with 29.6 mci of resin microsphere from the same catheter location that low-dose Y90 was administered. Repeat planar bremsstrahlung images were obtained and LSF was measured at 31% (**Figure 1B**). More importantly, the liver biodistribution of low and therapeutic dose Y90 depicted by SPECT/CT were also similar (**Figure 1C&D**). **This clinical example confirms significant overestimation of Y90 LSF using MAA and also illustrates the feasibility of identifying clinically significant LSF's using planar Y90 bremsstrahlung.**

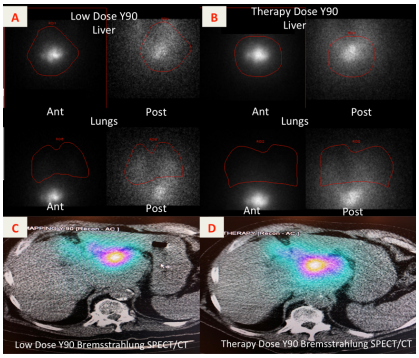


Figure 1 demonstrating a clinical case example in which low-dose Y90 was successfully imaged using planar and SPECT bremsstrahlung (A&C) with similar biodistribution to therapy dose Y90 (B&D).

B) A 37-year-old female with chemo-refractory metastatic breast cancer to the liver was referred to IR for Y90 radioembolization by a multidisciplinary tumor board. Her LSF on MAA shunt study was 4.3%. After resin Y90 RE therapy, planar and SPECT/CT bremsstrahlung scans were obtained. Y90 LSF after RE was less than 1% using scatter correction method and 12.1 % without scatter correction (**Figure 2**). **This case demonstrates the need for quantitative techniques if Y90 bremsstrahlung is to be used for LSF calculation.**

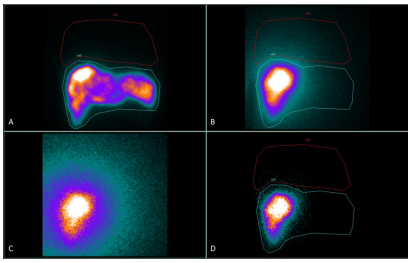


Figure 2 shows Tc-99m MAA image used for original shunt calculation (A), Y-90 bremsstrahlung image without scatter correction (B), Y-90 image in separate energy window used to calculate scatter in A(C), Y-90 image after scatter correction(D).

2.2.2 Correlative Studies Background

An anthropomorphic torso phantom with lung and liver compartments (Data Spectrum Corporation, Durham, North Carolina) was used to assess low-dose imaging capabilities with Y90 (**Figure 1**). Initially, 10.9 mCi of liquid Y90 HCL was injected into the liver compartment with an additional 2.9 mCi in two fillable spheres mounted in the liver to simulate liver tumors. Total liver activity was 13.8 mCi. Lung compartments were filled with a mixture of Styrofoam beads and a Y90 HCL solution with a total activity of 1.12 mCi. **This gave a true LSF of 7.5% and a TNR of 10.** The phantom was imaged using our planar imaging protocol for shunt calculations and with our SPECT/CT protocol for Y90. Energy windows were chosen for quantitative Y90 Bremsstrahlung imaging. Planar imaging (as clinically used for the MAA shunt studies) yielded 6.4% LSF. On the other hand, SPECT calculation of the lung shunt was 6.9%. SPECT/CT depicted the distribution of activity in the phantom and gave TNR of 6. The PET/CT images on the other hand had very few counts in both the liver and lungs due to the small number of positron emissions by low-dose Y90. Nevertheless, the TNR measured by PET was very accurate at 10 and the LSF was measured at 4.9%. **As depicted by our phantom study results, each imaging modality in the setting of low-dose Y90 have advantages and disadvantages. While PET appears to be accurately measuring TNR, Bremsstrahlung SPECT appears to be more accurate in estimating LSF. Our goal through the proposed study is to ultimately optimize and validate low-dose Y90 PET and/or SPECT as the single study needed to accurately plan Y90 therapy based on institutional availability.**

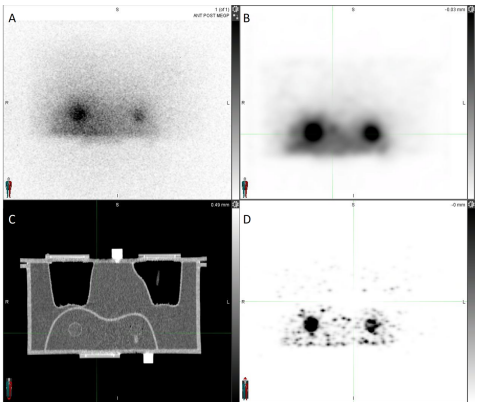


Figure 1 shows images used in the phantom analysis: A) Planar (static image), B) SPECT coronal, C) CT coronal, D) PET coronal.

2.3 Potential Risks and Benefits

Potential Risks:

As with any Y90 radioembolization, the potential risks involved includes liver failure, non-target embolization resulting in stomach or duodenum/proximal jejunum inflammation or ulceration. Additionally, radiation induced lung disease is a potential risk of Y90 radioembolization. With accurate mapping and treatment planning, which is standard of care, the risk of either liver failure, non-target embolization or radiation induced lung disease are significantly less than 1%. Related to angiography, there is risk of vascular injury and bleeding either at the access site or at the celiac access or SMA (in case of replaced or accessory right hepatic artery). The risk of clinically significant vascular injury or bleeding requiring another intervention is less than 1%.

Additional angiographic and low dose CT scans of the PET/CT and SPECT/CT in this study also involve ionizing radiation with risk factors primarily related to increased chance of cancer

development in the future. However, give the amount of radiation involved, the risk of quite minimal. Of note, the study has already been approved by radiation safety committee at Emory.

Potential Benefits:

More accurate treatment planning with low-dose Y90 can result in maximizing dose delivery to the tumor while minimizing radiation dose to the non-tumoral liver and lungs.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To compare the safety and accuracy/efficacy of low dose Y90 resin microspheres and MAA in predicting the actual dose delivered to the tumor, liver, and lung after Y90 therapy.	• Safety: adverse events related to Y90 radioembolization and angiography will be document by physical examination, clinical laboratory test and cross-sectional imaging. • Accuracy/Efficacy: The accuracy/efficacy of MAA as a predictor of therapeutic Y90 distribution will be compared to that of low-dose Y90.
Secondary	
1. To Identify tumor dose response thresholds (TDRT) and tumor dose distribution in patients with HCC treated with Y90 resin microspheres. ***2.*** **To optimize low dose Y90 techniques in predicting TNR and LSF.**	• Imaging Modified Response Criteria in Solid Tumors (m-RECIST) will be used on follow-up multiphase CT or MRI at 1, 3 and 6 months post Y90 radioembolization • Tumor dose response threshold will be determined • Imaging parameters for both Y90 SPECT and PET in both low and therapeutic dose will be optimized with the goal of recommending one of either SPECT or PET as the feasible imaging modality of choice at the conclusion of the study.

4. STUDY DESIGN

4.1 Overall Design

This study is a single arm phase II prospective clinical trial in which patients with HCC who are deemed suitable for Y90 radioembolization will be recruited. Patients will undergo standard of care mapping study with ^{99}TC-MAA to plan for Y90 radioembolization therapy. The additional, non-standard of care, intervention will be to do a second mapping study using low-dose Y90 (15 mCi) before the therapeutic Y90 radioembolization.

The distribution of MAA in terms of lung shunt fraction (LSF) and tumor to normal liver activity ration (TNR) will be compared to that of low-dose Y90. The treatment planning will be performed using standard of care MAA biodistribution using partition dosimetry model.

After administration of therapeutic Y90 dose, the actual dose delivered to tumor, non-tumoral liver (NTL) and lungs will be compared to the dose predicted by MAA and low-dose Y90.
The patients will be the followed-up clinically and with imaging at 1, 3 and 6 months to determine tumor response, potential treatment related toxicity and to determine TDRT.

Hypothesis: **Low dose Y90 microspheres as the treatment planning radiotracer will allow more accurate prediction of therapeutic Y90 liver biodistribution, which will enable us to perform prospective personalized dosimetry for every individual patient.**

The results of this study will determine the safety and efficacy of using low dose Y90 as a direct surrogate for treatment planning to ensure delivering cytotoxic Y90 dose to the targeted tumor(s), while concomitantly minimizing liver and lung toxicity with more accurate prediction of therapeutic Y90 biodistribution. **Our long-term objective is to increase the likelihood of objective tumor response, prolonged progression-free survival (PFS) and overall survival (OS) in patients with HCC treated with Y90 RE.**

The study is a single-arm in study in which each patient will undergo two sets of mapping procedure before the actual Y90 therapy. One with standard of care ^{99}Tc-MAA and one with low-dose (15 mCi) Y90 microspheres. **Therefore, the additional intervention in the study is the second mapping procedure with low-dose Y90 microspheres.** Each patient will be used as their internal control to minimize selection biases. **Additional to standard of care Y90 SPECT/CT after therapy, the patient will undergo one PET/CT after low-dose Y90 and one PET/CT after Y90 therapy.**

The study is a single center (Emory) single site study. For the convenience of patients and in order to obtain additional PET/CT's on the same day as the mapping and Y90 therapy on a state-of-the-art PET scanner, all mapping and therapy procedures for each patient will be performed at either Emory University Hospital Midtown or Emory University Hospital.

The remainder of the study will be standard of care will imaging and clinical follow-up at 1,3, 6 months in IR clinics. Additionally, patient will be follow-up by phone at 1-week post therapy. The data analysis in terms of the actual dose delivered to the tumor, NTL and lung and the accuracy of MAA vs. low-dose Y90 to predict the respective doses will not require additional patient visits.

4.2 Scientific Rationale for Study Design

As discussed in detail in 2.1, there is growing evidence that factoring individual patient characteristics into Y90 treatment planning are likely to significantly impact both TR and treatment tolerability. To this end, the partition model, while more resource intensive, has made great strides towards treatment individualization. However, the use of MAA in predicting post Y90 RE absorbed dose and biodistribution is flawed and inaccurate, leading to suboptimal dose delivery, unnecessary hepatotoxicity and poor outcomes. **Therefore, we propose low-dose Y90 microspheres for therapy planning, as an alternative to MAA, to be a bioidentical therapeutic Y90 surrogate marker to better predict and thus achieve optimal therapeutic dosing.** Our long-term goal is to improve TR, PFS, and OS while reducing potential associated toxicities in patients treated with Y90 RE.

4.3 Justification for Dose

Based on our phantom study to minimize scatter on SPECT/CT and to ensure adequate activity to be imaged using PET, 15 mCi of low-dose Y90 is found to be adequate. Additionally, in a hypothetical patient with a LSF of 100% (usually ~10% in HCC patients), 15 mCi of Y90 activity will result in 27.8 Gy of radiation to the lungs which is within the accepted limits of 30 Gy per treatment session. Such patient will not be a candidate a for therapeutic Y90 dose so cumulative dose to the lungs will remain below 30 Gy.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5. STUDY POPULATION

5.1 Inclusion Criteria

Study candidates must meet all of the following inclusion criteria to be eligible for participation in this study:

a. Adults ≥ 18 years
b. Life expectancy of 6 months or more as determined by the investigator
c. HCC confirmed by Liver Reporting & Data System (LIRADS) on MRI or CT
d. Must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with CT scan, MRI, or calipers by clinical exam. See Section 12 (Measurement of Effect) for the evaluation of measurable disease.
e. ≤3 lesions
f. Longest dimension of the largest lesion ≤7cm
g. Single lobe disease
h. No significant extrahepatic metastatic disease
i. Barcelona Clinic Liver Cancer Stage A, B or C
j. ECOG < 2 (Appendix A)
k. Lesion(s) <50% of liver volume
l. Bilirubin ≤ 2 mg/dL
m. Albumin ≥ 3 g/dL
n. PT/INR < 2
o. AST/ALT ≤ 3 institutional upper limit of normal (ULN)
p. Platelet count > 50,000/mcL
q. Lung shunt fraction of <20% by planar MAA if dose modification results in inadequate dose delivered to the tumor(s)
r. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
s. Completion of all previous therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer ≥ **12** week before the start of study therapy.
t. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.

u. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.
v. The effects of *Y90 microspheres* on the developing human fetus are unknown. For this reason female of child-bearing potential (FCBP) must have a negative serum or urine pregnancy test prior to starting therapy.

w. FCBP and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of *[IND Agent]* administration. A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.

5.2 Exclusion Criteria

An individual who does not meet all the inclusion criteria in section 5.1.

6. REGISTRATION PROCEDURES

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

6.1 Local Winship Procedures

Study personnel will notify Winship Central Subject Registration (WCSR) by email at [redacted] once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System ([redacted] Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

6.2 Enrollment / Randomization and Blinding

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.

When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and or enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

7. STUDY INTERVENTION

7.1 Agent Administration (or Study Intervention Administration)

7.1.1 Study Intervention Description

The low-dose Y90 (15 mCi), will remain the same for all the patients. As explained in section 4.3, this dose ensures adequate imaging on both SPECT and PET without the risk of developing radiation induced pneumonitis in the setting of high LSF.

The therapeutic dose of Y90 will be calculated using the partition model detailed below based MAA biodistribution in the tumor, non-tumoral liver and the lungs.

7.1.2 Dosing and Administration

Treatment will be administered on an *outpatient* basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 8. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

No dose escalation or dose expansion is planned in this procedure.

The treatment Y90 dose will be calculated using the partition model as detailed below:

The required therapeutic Y90 dose will be calculated using MAA SPECT, Y90 SPECT and Y90 PET. **Although all 3 sets of calculations will be made prospectively, the activity calculation based on MAA SPECT (the standard of care) will be used for actual treatment planning.** The activities calculated using Y90 SPECT and PET will be used for post-hoc analysis. Partition model to achieve cytotoxic Target Tumor Dose of >100 Gy will be utilized using the following formulas[7]:

1) **Desired Tumor Activity (GBq) = (100 Gy X Tumor Mass (Kg)) / 50**
2) **Targeted Normal Liver Activity (GBq) = Desired Tumor Activity (GBq) / TNR**
3) **Targeted Liver Lobe Activity (GBq) = (Targeted Normal Liver Activity + Desired Tumor Activity) (GBq)**
4) **Targeted Liver Lobe Dose (Gy) = Targeted Liver Dose Activity (GBq) X 50 / Liver mass (Kg)**

The liver and tumor mass will be determined using the volumes calculated by MIM software and assuming density of 1.03 g/cm^3 [39]. It will be ensured that targeted liver dose remains below 50 Gy which has been shown to be safe with no sequela of radiation induced liver disease while ensuring the target tumor dose >100 Gy[7, 26].

5) **Y90 Activity for administration (GBq) = Targeted Liver Lobe Activity (GBq) X (1+LSF)**

Lung dose after therapeutic Y90 RE will be calculated using the following formula:

6) **Lung Dose (Gy) = Y90 Activity to be Administered (GBq) X LSF X 50 / Mass of Lungs (Kg)**

Lung Dose <30Gy will be ensured by reducing administered activity if needed (lung mass assumed at 1 Kg)[8].

The MAA, low-dose and therapeutic dose Y90 microspheres will be administered intra-arterially using the following technique:

Radial or femoral arterial access will be obtained. A 5 Fr catheter will be used to select superior mesenteric artery and celiac trunk. A 2.8 Fr microcatheter will be advanced to the right or left hepatic artery branch supplying the targeted HCC lesion(s). From this location, detailed evaluation of hepatic arterial vasculature using conventional angiography and 3D cone beam CT (CBCT) will be performed to ensure complete perfusion of the targeted tumor(s) and absence of visible non-target embolization. If a potential non-target vessel (i.e. gastroduodenal or right gastric artery) is observed, the vessel will be embolized using coils or plugs during the first mapping study using MAA. From the catheter location where CBCT will be performed to ensure complete perfusion of the tumor and lack of non-target supply. Then MAA, low-dose or therapeutic dose Y90 will be administered.

7.1.3 Dose Modifications

In patients with LSF of ≥ 20%, the therapeutic dose to the tumor will be modified to ensure <30 Gy to the lungs while maintaining >100 Gy to the tumor if possible.

7.2 Agent Preparation/Handling/Storage/Accountability

7.2.1 Acquisition and accountability

The radiopharmaceutical (Y90) provided for this study will be used only as directed in the study protocol. A trained certified nuclear medicine personnel at EUH or EUHM will receive the shipment and monitor the shipment box as per standard everyday clinical protocols set by Emory Radiation Safety Office. Study site personnel will account for all radiopharmaceutical received at the site. As per protocol, all radioactive materials in nuclear medicine departments will be stored in secure locked hot labs in accordance with the conditions specified on the labels. Dr. Galt will maintain an accurate record of dispensing the study radiopharmaceutical in a Drug Accountability Log.

The Drug Accountability Log will record specifics to study drug dispensation such as:

- Records of product delivery, inventory, temperature monitoring, destruction, and return.
- Dosages prepared, time prepared, doses dispensed.
- Doses and/or vials destroyed.

• The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.
Drug accountability will be noted by the field monitor during site visits and at the completion of the study.
This information must be captured in the source document at each patient visit. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

7.2.2 Formulation, Appearance, Packaging, and Labeling

Each hot lab at EUH or EUHM have their own ^{99}Tc generator which will be labelled with MAA according to standard clinical protocol used on a daily basis. The Y90 resin microspheres vials will be delivered at 196 mCi activity on Monday.

7.2.3 Product Storage and Stability

All radioactive materials including ^{99}Tc-MAA and Y90 microspheres will be stored in secure locked hot labs at nuclear medicine departments at EUH or EUHM.

7.2.4 Preparation

Each hot lab at EUH or EUHM have their own ^{99}Tc generator which will be labelled with MAA according to standard clinical protocol used on a daily basis.

15 mCi of Y90 will be drawn from the 196 mCi vial on Monday to use for the mapping study. The remainder of the 181 mCi activity will decay to 83 mCi by Thursday (Y90 half-life = 64.1 hours). The mother vial will be stored in a clean secure place in hot lab with sterile alcohol swab or paraffin placed on the diaphragm of the vial. After prospective therapeutic dose calculation detailed above, the appropriate activity will be drawn from the mother vial.

7.3 General Concomitant Medication and Supportive Care Guidelines

Patients on vascular endothelial growth factor (VEGF) inhibitors will hold their VEGH inhibitors for 4 weeks prior to mapping angiography. They may resume their medication after Y90 therapy.

7.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded. In

general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed.

• Medications to prevent or treat nausea or vomiting. • Anti-diarrheal medications (e.g., loperamide) for patients who develop diarrhea. • Pain medication to allow the patient to be as comfortable as possible. • Treatment with bisphosphonates or denosumab for pre-existing, painful bone/liver metastases, and limited-field palliative radiotherapy or surgery is permitted. Patients requiring initiation of such treatment during the course of the study must be evaluated for disease progression; radiotherapy like any concomitant medication must be listed on the CRF.

• Immunosuppressive agents to treat suspected irAEs • Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents as per local or published guidelines; in case of anemia, thrombocytopenia or neutropenia, potential immune mediated etiology should be ruled out • Nutritional support or appetite stimulants (e.g. megestrol). • Oxygen therapy and blood products or transfusions. • Inactivated vaccines. • The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

7.3.2 **Prohibited Concomitant Medications**

During the course of the study, patients must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) or any other therapies that may be active against cancer or modulate the immune responses. However, limited-field palliative radiotherapy may be allowed as concomitant therapy (see above). The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, and for prophylaxis against imaging contrast dye allergy, standard pre-medication for chemotherapy or replacement-dose steroids in the setting of adrenal insufficiency (providing this is < 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as COPD requiring treatment. If systemic corticosteroids are required for the control of infusion reactions or irAEs, it must be tapered and be at non-immunosuppressive doses (< 10 mg/day of prednisone or equivalent) before the next administration of study treatment. If the dose of prednisone or equivalent cannot be reduced to less than 10 mg/day before the administration of next dose of study treatment then the study agent must be discontinued. The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed. There are no prohibited therapies during the post-treatment follow-up period.

7.3.3 **Rescue Medications & Supportive Care**

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be

followed up for adverse events and serious adverse events until start of new antineoplastic medication or 150 days after discontinuation of study drug, whichever is sooner. Suspected SAEs will continue to be collected beyond the 150-Day safety visit. This will be done by return clinic visits, laboratory checks, and phone calls. The emergence of Immune-Related AE (irAE) may be anticipated based on the mechanism of action of immunomodulatory therapies. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator to verify the immune-related nature of the AE and to exclude alternative explanations. Recommendations have been developed to assist investigators in assessing and managing the most frequently occurring irAEs.

7.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), patients will be treated and followed for 6 months as part of the clinical trial and then at 3 months interval after as per standard of care at Emory IR. This will generally continue until patient's death, enrollment in hospice or loss to follow-up. If there is tumor progression at 3 months, patient may ensue other liver directed or systemic therapies.

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

7.4.1 Treatment Beyond Progression

In this study, patient will only be treated once unless the entire tumor is covered by the initial Y90 radioembolization therapy. In that case, the patient will undergo a second Y90 therapy in 4 weeks assuming eligibility criteria are maintained. If there is tumor progression at 3 months, patient may ensue other liver directed or systemic therapies.

7.5 Duration of Follow Up

Patients will be followed for approximately 180 days after Y90 therapy according to the SoA's detailed above to determine both safety and efficacy. The patients will then be followed every 3 months as per standard of care at Emory IR. This will generally continue until patient's death, enrollment in hospice or loss to follow-up.

Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination. In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.6 Discontinuation of Study Intervention

Discontinuation from low-dose Y90 mapping study does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).
Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. The EOT visit will occur 30 days after the last dose of the radiopharmaceutical administration.

Reasons for EOT are:
• PD in the absence of clinical benefit as determined by the Investigator.
• Occurrence of a clinically significant AE found to be unacceptable or non-resolution of clinically significant AEs for > 6 weeks.
• Symptomatic deterioration.
• Achievement of maximal response.
• Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor.
• Continued participation is no longer in the patient's best interest in the opinion of the Investigator.
• Withdrawal of consent.

Patient remain on treatment phase until discontinuation of all study drugs, In the event of a patient's withdrawal, the Investigator will promptly notify the Sponsor and make every effort to complete the EOT procedures specified in the Schedule of Events. The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are assigned but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are assigned and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

The data to be collected at the time of study intervention discontinuation will include the following: the reason for discontinuation and any imaging and laboratory follow-up.

7.7 Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive Y90 therapy

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and subsequently withdraw, or are withdrawn or discontinued from the study will be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

All patients will undergo baseline liver mass protocol abdominal MRI without and with contrast within 30 days prior to the shunt study, and 1, 3, 6, and 12 months after Y90 RE therapy. Objective TR will be evaluated longitudinally using mRECIST criteria by Dr. Kokabi with a help of an abdominal radiologist. TDR will be calculated using two different methods: 1. Mean dose of the entire tumor resulting in objective TR; 2. Determination of % tumor volume receiving >100 Gy resulting in objective TR. The reason for the second TDR calculation is to take into account the non-homogeneity of Y90 dose delivered to the tumors previously reported.[27, 28] TDR threshold based on logistic regression will be determined by Drs. Kokabi and Risk.

Additional scan assessments may be collected based on clinical symptoms, as appropriate. Documented tumor measurements are required using CT scans, MRI, physical examination, and/or digital photography, as appropriate. Any imaging used to assess disease at any time point will be submitted for an independent radiology review. The same method of assessment (CT or MRI and/or digital photography) and the same technique for acquisition of images must be used for all

study assessments (contrast must be used unless medically contraindicated). Baseline imaging should be done at the same institution/facility which will be used to measure response during the patient's participation in the study. Radiographic assessments and efficacy analyses will be conducted by the Investigator site as well as the independent radiology review committee.

8.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

Screening Phase

Screening procedures will be performed up to 14 days prior to enrollment and initiation of Y90 therapy as applicable, except for baseline imaging (up to 28 days allowed) unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- Review of prior/concomitant medications
- Imaging by CT/MRI
- Clinical laboratory tests for:
    - Hematology
    - Complete Metabolic Panel (CMP)
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum or urine pregnancy test (for women of childbearing potential)

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3). Screening procedures performed within 7 days of mapping do not need to be repeated on mapping day.

A. Pre-procedure evaluation on Mapping day (Monday)

- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs
- Review of prior/concomitant medications
- Clinical laboratory tests for:
  - Hematology
  - CMP
  - Serum pregnancy test (for women of childbearing potential)

B. 1st Mapping Angiography and Administration of ^{99m}Tc MAA (Monday)

The shunt studies will be performed by Dr. Kokabi on Mondays for reasons explained below. Radial or femoral arterial access will be obtained. A 5 Fr catheter will be used to select superior mesenteric artery and celiac trunk. A 2.8 Fr microcatheter will be advanced to the right or left hepatic artery branch supplying the targeted HCC lesion(s). From this location, detailed evaluation of hepatic arterial vasculature using conventional angiography and 3D cone beam CT (CBCT) will be performed to ensure complete perfusion of the targeted tumor(s) and absence of visible non-target embolization. If a potential non-target vessel (i.e. gastroduodenal or right gastric artery) is observed, the vessel will be embolized using coils. From the catheter location where CBCT was performed, 4 mCi of Tc^{99m} MAA will be administered. **The catheters will be removed, and the arterial access sheath will be secured in place. This is commonly done for our out of town or out of country patients at Emory in whom both mapping and Y90 is performed on the same day. Before the patient leaves the IR suite, all the catheters will be removed. The sheath is gently sutured to the overlying skin. Multiple tegaderms will be applied. Additionally, for the radial access cases, an arm-board will be applied. When taking all the pre-cautions detailed above, we have not experienced any accidental dislodgment during patient transport/waiting.** The patient will be then transferred to nuclear medicine department for ^{99m}Tc MAA planar and SPECT/CT of the chest and abdomen.

C. ^{99m}Tc MAA Planar and SPECT/CT of chest and abdomen (Monday)

Planar and SPECT/CT of chest and abdomen will be obtained with low energy filter according to our standard clinical protocol at Emory. The patient will be then transferred back to IR for 2nd mapping angiography and administration of low-dose Y90. **Quantitative reconstruction of SPECT/CT with Tc-99m is available with MIM Software[40].**

D. 2nd Mapping Angiography and Administration of low dose Y90 (Monday)

Fifteen (15) mCi of resin microsphere will be drawn from a 5-day flex dose vial containing approximately 196 mCi of activity. Dr. Galt will oversee the extraction of the low dose by nuclear medicine technologists. The patient will be brought back to IR on the same day (Monday). Using the technique detailed above, the same hepatic artery branches where MAA injection was performed will be selected. From this location, 15 mCi of resin Y90 microspheres will be administered. **After the procedure, patient's femoral sheath will be removed and hemostasis will be achieved with manual compression or closure device. If procedure performed via radial access, which is more commonly performed currently at Emory, the radial sheath will stay in and removed according to IR protocol after Y90 SPECT/CT.**

The remainder of the activity will be used for therapy on Wednesday/Thursday of the same week depending on the desired dose. The patients will be then transferred to nuclear medicine department for planar and SPECT/CT bremsstrahlung imaging of the chest and abdomen on the same day.

E. Low-dose Y90 Planar and SPECT/CT of chest and abdomen (Monday)
Quantitative reconstruction of Y90 bremsstrahlung SPECT/CT will follow the procedures outlined by Siman et al[41].When low dose Y90 bremsstrahlung follows administration of Tc-99m on the same day, the procedures of Siman et al have to be adapted by choosing an energy window for the bremsstrahlung imaging with a minimum energy of 160 keV, avoiding contamination of the image by Tc-99m 140 keV photons. Calibration of the quantitation method for the adapted energy windows is accomplished through comparison of the images of Y90 bremsstrahlung obtained with the standard and adapted energy windows[41].

Please note that this is commonly performed at Emory for our out of town or international patients in whom both mapping and Y90 therapy is performed on the same day. Since only the proportion of activity in each compartment (i.e. tumor, liver and lung) are needed to calculate dose delivered in the setting of known administered activity, filter any energy less than 160 keV will result in accurate quantification of Y90 dose delivered. **Additionally, patient will undergo PET/CT on the same day using a state-of-the-art PET scanner which will only detect Y90 activity without any noise from MAA. This will be used as an additional step to confirm our hypothesis that same MAA and Y90 is feasible.**

The patient will then be discharged from IR after removal of the radial sheath according to our standard protocol.

F. Low-dose Y90 PET/CT of chest and abdomen (Monday)
The patient will then undergo time of flight Y90 PET/CT with one or two bed positions depending on the patient's size. This will also occur on the same day and at the same location as the remainder of mapping day either at EUH or EUHM.

Schedule of Mapping Days:

7:30 AM-9:30 AM: 1st Angiographic study for mapping and MAA delivery

10:00 AM-11:00 AM: MAA SPECT/CT (Patient will go to nuclear medicine with radial/femoral arterial access sheath in place)

11:30 AM-1:00 PM: 2nd Angiographic study for low-dose Y90 delivery (After the procedure, patient's femoral sheath will be removed and hemostasis will be achieved with manual compression or closure device. If procedure performed via radial access, which is more commonly performed currently at Emory, the radial sheath will stay in and removed according to IR protocol after Y90 SPECT/CT.)

2:00 PM-3:00 PM: Y90 Bremsstrahlung SPECT/CT

3:00 PM-3:30 PM: Removal of the radial sheath at IR post procedural area and discharge.

4:30-5:30 PM: Y90 PET/CT.

Patient is free to go home after this.

G. Prospective Personalized Targeted Therapeutic Y90 Tumor(s) Dosimetry (Tuesday/Wednesday)

The required therapeutic Y90 dose will be calculated using MAA SPECT, Y90 SPECT and Y90 PET. **Although all 3 sets of calculations will be made prospectively, the activity calculation based on MAA SPECT (the standard of care) will be used for actual treatment planning.** The activities calculated using Y90 SPECT and PET will be used for post-hoc analysis. Partition model to achieve cytotoxic Target Tumor Dose of >100 Gy will be utilized using the following formulas[7]:

i. **Desired Tumor Activity (GBq) = (100 Gy X Tumor Mass (Kg)) / 50**
ii. **Targeted Normal Liver Activity (GBq) = Desired Tumor Activity (GBq) / TNR**
iii. **Targeted Liver Lobe Activity (GBq) = (Targeted Normal Liver Activity + Desired Tumor Activity) (GBq)**
iv. **Targeted Liver Lobe Dose (Gy) = Targeted Liver Dose Activity (GBq) X 50 / Liver mass (Kg)**

The liver and tumor mass will be determined using the volumes calculated by MIM software and assuming density of 1.03 g/cm^3 [39]. It will be ensured that targeted liver dose remains below 50 Gy which has been shown to be safe with no sequela of radiation induced liver disease while ensuring the target tumor dose >100 Gy[7, 26].

v. **Y90 Activity for administration (GBq) = Targeted Liver Lobe Activity (GBq) X (1+LSF)**

Lung dose after therapeutic Y90 RE will be calculated using the following formula:

vi. **Lung Dose (Gy) = Y90 Activity to be Administered (GBq) X LSF X 50 / Mass of Lungs (Kg)**

Lung Dose <30Gy will be ensured by reducing administered activity if needed (lung mass assumed at 1 Kg)[8].

H. 3rd Angiography and Administration of Y90 Therapy Dose (Wednesday/Thursday)

The actual prescribed Y90 activity as calculated above using MAA SPECT (**the current standard of care)** will be administered on Wednesday or Thursday of the same week after the shunt study. The desired activity will be drawn from the remainder of activity in the 5-day flex resin microsphere vial. It will be administered by Dr. Kokabi using the same catheter techniques described above. **After the procedure, patient's femoral sheath will be removed and hemostasis will be achieved with manual compression or closure device. If procedure performed via radial access, which is more commonly performed currently at Emory, the radial sheath will stay in and removed according to IR protocol after Y90 SPECT/CT.** The patient will be then transported to nuclear medicine department of Y90 SPECT/CT.

I. Therapeutic-dose Y90 Planar and SPECT/CT (Wednesday/Thursday)

Using the same technique described above (section E), planar and SPECT/CT will be performed using medium energy filter. The patient will then be discharged from IR after removal of the radial sheath according to our standard protocol.

J. Therapeutic-dose Y90 PET/CT of chest and abdomen (Wednesday/Thursday)

The patient will then undergo time of flight Y90 PET/CT with one or two bed positions depending on the patient's size. This will also occur on the same day and at the same location as the remainder of mapping day either at EUH or EUHM.

Below is the conservative estimated timeline of Mapping/shunt studies performed on Wednesday or Thursday:

11:00 AM-12:30 PM: 3rd angiographic study to deliver therapeutic dose of Y90.

1:00 PM-2:00 PM: Y90 Bremsstrahlung SPECT/CT (After the procedure, patient's femoral sheath will be removed and hemostasis will be achieved with manual compression or closure device. If procedure performed via radial access, which is more commonly performed currently at Emory, the radial sheath will stay in and removed according to IR protocol after Y90 SPECT/CT.)
3:00 PM-3:30 PM: Removal of the radial sheath at IR post procedural area and discharge.

4:30-5:30 PM: Y90 PET/CT at Cardiac PET center on the 4th floor of EUHM.

Patient is free to go home after this.

K. Y90 Therapy Tumor, Liver, and Lung Dose Calculation (Friday)

Utilizing the MIM software, post Y90 therapy PET/CT data and partition method described above, the mean actual dose delivered to the tumor, normal liver, and lung will be calculated by Drs. Sethi and Kokabi. The software will generate ROIs from the inside to the periphery of the tumor based on Y90 delivery, and Dose Volume Histograms (DVH) plotting the delivered dose as a function of liver volume. Using DVH, % of tumor volume receiving >100Gy and dose range to the tumor will be also calculated.

L. Follow-up phone call [redacted] or study nurse (1-week post therapy)

Patient will be followed by phone to ensure they are doing well, and they will be screened for any symptoms related to adverse events. If any concerning symptoms is reported, they will be brought to IR clinic for further evaluation.

M. 1-Month clinical and Imaging Follow-up

- Multiphase liver mass protocol MRI or CT will be obtained
- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs
- Review of prior/concomitant medications
- Clinical laboratory tests for:
  - Hematology
  - CMP

N. 3-Month clinical and Imaging Follow-up

- Multiphase liver mass protocol MRI or CT will be obtained
- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs
- Review of prior/concomitant medications
- Clinical laboratory tests for:
  - Hematology
  - CMP

O. 6-Month clinical and Imaging Follow-up

- Multiphase liver mass protocol MRI or CT will be obtained
- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status

- Vitals signs
- Review of prior/concomitant medications
- Clinical laboratory tests for:
  - Hematology
  - CMP

End of Treatment

End of treatment is defined as the last planned Y90 therapy within the 6-month dosing period. For subjects who discontinue drug treatment prior to 6 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.
Assessments for subjects who have completed treatment and achieved disease control, or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Event.
All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

8.2 Description of study procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, day of mapping, day of Y90 therapy and beyond, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, heart, lungs, abdomen, extremities, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be reported at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry
- Coagulation parameters: Activated partial thromboplastin time and International normalised ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
    - Urine human chorionic gonadotropin (at screening only)
    - Serum beta-human chorionic gonadotropin

Hematology Laboratory Tests	
Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Clinical chemistry (serum or plasma) Laboratory Tests	
Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein

Clinical chemistry (serum or plasma) Laboratory Tests

Albumin	Glucose
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

[b] At baseline and as clinically indicated

9. MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using m-RECIST [42].

9.1 m-RECIST Criteria

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described in the following subsections.

For the purposes of this study, patients should be re-evaluated for response at 1, 3 and 6 months post Y90 therapy.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *Y90 therapy.*

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received Y90 therapy, and have had their disease re-evaluated 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 completion of study could be considered for alternate therapy after documentation of PD at 3 months.)

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 by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 5 lesions per treated liver lobe will be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of the size of their enhancing portion but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

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.

Multiphase Liver Mass Protocol CT and MRI: Liver mass protocol MRI is the preferred imaging modality in this study. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

FDG PET/CT: PET/CT is not an ideal modality for evaluation HCC at baseline or after therapy.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.1.1 Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.
When more than one measurable lesion is present at baseline, all lesions up to a maximum of 3 lesions total in the targeted liver lobe and 3 lesions in the non-target liver lobe and additionally 3 lesions outside of liver will be evaluated. We will use m-RECIST for the evaluation of liver lesions which is based on the size of enhancing portion of the lesions and not the entire size of the lesion. This has shown to be much more accurate in evaluation of HCC compared to RECIST and RECIST 1.1 [42].
Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further

characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. For assessment of abscopal response, any of the target lesions identified at baseline will be measured and followed for abscopal response. This target lesion should not be a target of injection or biopsy. The abscopal response is defined as a shrinkage of ≥ 20% from baseline in any target non-manipulated metastatic lesion identified at baseline.

Evaluation of Target Lesions

Complete Response (CR): No intramural arterial enhancement in all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of viable target lesions.

Stable Disease (SD): Features classifiable as neither partial response nor progressive disease.

Evaluation of Non-Target Lesions

Complete Response (CR): No intramural arterial enhancement in all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of viable target lesions.

Stable Disease (SD): Features classifiable as neither partial response nor progressive disease.

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).

9.1.2 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.

For Patients with Measurable Disease (*i.e.*, Target Disease)

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** 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.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

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 progressive 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, including the baseline measurements.

Progression-Free Survival

PFS is defined as the time from the date of first dose to the date of the first objectively documented progressive disease per m-RECIST or death, whichever is earlier. Patients who do not have the date of disease progression per m-RECIST or date of death will be censored on the date of the last evaluable tumor assessment. Patients who started a new antineoplastic regimen prior to disease progression per m-RECIST will be censored on the date of the last evaluable tumor assessment prior to receiving the new antineoplastic regimen. Patients whose disease progression or death appears after missing two consecutive tumor assessments will be censored on the date of the last evaluable tumor assessment. Patients who are lost to follow up will be censored on the date of their last evaluable tumor assessment. PFS will be estimated using the Kaplan-Meier method. The median and its 95% CI, along with the 25% and 75% quartiles will be summarized for all treated patients. OS will be defined as the date of first dose to the date of death. Patients who do not have a date of death will be censored on the last date for which the patient was known to be alive. OS will be analyzed similarly to PFS.

Response Review

All responses will be reviewed by an expert(s) independent of the study simultaneously as the results become available.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

Primary Objective Endpoints:

A) Accuracy/Efficacy: The accuracy/efficacy of MAA as a predictor of therapeutic Y90 distribution will be compared to that of low-dose Y90.

H_0: Y90 will have the same LSF as MAA.

H_A: Y90 will have significantly less LSF than MAA.

H_0: Y90 will have the same TNR as MAA.

H_A: Y90 will have significantly higher TNR than MAA.

B) Safety: adverse events related to Y90 radioembolization and angiography will be document by physical examination, clinical laboratory test and cross-sectional imaging.

No statistical consideration applied to the safety portion of the primary end point as it is a single arm study in which every patients undergo both mapping procedures with MAA and low-dose Y90. Detailed safety analysis plan is outlined below in section 10.5.

10.2 Sample Size/Accrual Rate

Based on previously published data by our group, we assume mean (SD) LSF of 11.66% (10.2) for HCC using MAA[43]. Assuming LSF in low-dose Y90 is 50% lower than what is predicted by MAA and within subject correlation of 0.5 in a paired t-test, **n=30** achieves 80% power with α=0.05. This assumption is based on several previously published studies including the work presented by our own that demonstrate that MAA overestimates true Y90 LSF by as high as 100% [25, 35-37]. Assuming mean (SD) TNR of 5.4 (2.1) using MAA is 30% lower than low-dose Y90, the power achieved with n=30 is greater than 99% [8, 25].

Emory University Hospital is one of the busiest liver transplant and cancer centers in United States. Annually, 150 HCC patients who may be transplant/surgical or palliative therapy candidates are referred to interventional radiology (IR) at Emory for liver directed therapies. Assuming a conservative accrual rate of 30%, we predict an enrollment of **n=30** patients in 6-8

months. In the event that a patient drops out either after being consented or after having a part of the study completed, a new patient will be recruited.

10.3 Analysis of Primary Endpoints

Summary statistics will be estimated for all variables collected. Continuous variables will be presented as means, standard deviation, and range. Categorical variables will be summarized with frequencies and percentages. To assess the correlations between categorical clinical factors and numerical variables, t-test or ANOVA tests were conducted when data followed a normal distribution, otherwise Wilcoxon rank sum test or Kruskal-Wallis test were used instead. Pearson correlation coefficients were calculated to measure the correlation between two numerical variables, and the significance of coefficients were tested using Wald's test.

The primary endpoints are LSF and TNR for accuracy efficacy of the treatment. In the primary analyses, LSF and TNR will be estimated and compared between the two groups (MAA vs Y90) using two sample student's paired t-test. General linear model (GLM) will be further used in the multivariable analysis to estimate the adjusted efficacy of treatment (MAA vs Y90) on LSF and TNR after adjusting for other factors, respectively.

10.4 Analysis of Secondary Endpoints

1. **To Identify tumor dose response thresholds (TDRT) and tumor dose distribution in patients with HCC treated with Y90 resin microspheres.**

All patients will undergo baseline liver mass protocol abdominal MRI without and with contrast within 30 days prior to the shunt study, and 1, 3, 6, and 12 months after Y90 RE therapy. Objective TR will be evaluated longitudinally using mRECIST criteria by Dr. Kokabi with a help of an abdominal radiologist. TDR will be calculated using two different methods: 1. Mean dose of the entire tumor resulting in objective TR; 2. Determination of % tumor volume receiving >100 Gy resulting in objective TR. The reason for the second TDR calculation is to take into account the non-homogeneity of Y90 dose delivered to the tumors previously reported.[27, 28] TDR threshold based on logistic regression will be determined by Drs. Kokabi, Zhen, and Risk.

2. **To optimize low dose Y90 techniques in predicting TNR and LSF.**

No statistical consideration was deemed necessary for this secondary endpoint.

10.5 Safety Analyses

Adverse event data will be described and graded per the NCI CTCAE 5.0 guidelines. For each adverse event, information to be collected includes event description, time of onset, clinician assessment of severity, relationship to study product (assessed only by those with the training and

authority to make a diagnosis), and time of resolution/stabilization of the event. Regardless of relationship, all AEs will be recorded with start dates occurring any time after patient receives Y90 until 7 (for non-serious AEs) or 100 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. Adverse events will be summarized and described within each cohort. They will initially be reviewed regardless of attribution, but also whether they are possibly, probably, or definitely related to treatment. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be related" to study treatment in the event of an actual relationship developing. The incidence of severe adverse events or toxicities will be described. We will assess the proportion of patients who experience grade 3 or higher non-hematologic toxicity. To assess tolerability, we will also capture the proportion of patients who go off treatment due to adverse events.

10.5.1 **Baseline descriptive statistics**

The following baseline descriptive statistics will be performed:

1. Mean and Median Age and standard deviation
2. Frequency of Male vs. Female
3. Frequency of underlying cause of cirrhosis: Hepatitis B, Hepatitis C, Alcohol, NASH, others, no cirrhosis.
4. Mean and Median maximal tumor diameter for index tumor with standard deviation
5. Mean and Median number of lesions with standard deviation

10.5.2 **Planned interim analyses (if applicable)**

N/A

10.5.3 **Analysis of efficacy endpoints**

Responders will be defined as those that achieve partial response (PR). CR rate will be calculated with an exact 95% confidence interval, both within cohorts but not between cohorts. CR rate will be calculated among eligible patients who are evaluated for response at the 90-day and 180-day assessments; patients who fail to have a response assessment due to early progression or death will also be considered evaluable for response and categorized as non-responders.

Patients who fail to have a response assessment for other reasons (e.g., refusal due to travel constraints) will be considered unevaluable and will not be included in the denominator when calculating CR rate. Patients will be analyzed in the cohort to which they were enrolled.

The number and percentage of subjects experiencing objective response will be descriptively summarized overall and by cohort. Frequencies and percentages will be used to summarize these endpoints.

10.5.4 **Analysis of secondary endpoints**

Secondary clinical endpoints will be evaluated to assess outcomes including biology of resistance and survival. The endpoints with their definitions are listed as follows:

1. Tumor Dose Response Threshold (TDRT): defined as the Y90 dose that results in CR or PR
2. Tumors with LD 50 and LD 70: Defined at frequency of tumors in which 50% or more or 70% or more of their volume received above TDRT and their correlation with response.
3. Time to progression (TTP): defined as the time from start of protocol therapy until the criteria for disease progression are met. Patients who are either lost to follow-up, die or who begin alternative treatments prior to progression, will have their data censored as of the date considered to be lost to follow-up, date of death, or the first day of alternative therapy.
4. Progression-free survival (PFS): defined as the time from start of protocol therapy to disease progression or death from any cause, censoring patients without an event at time of last clinical assessment.
5. Overall survival (OS): defined as the time from start of protocol therapy to death, censoring patients who are alive at last follow-up

Protocol therapy related toxicities rate will be summarized using descriptive statistics such as frequencies and proportions. Differences in the proportion of patients who experience protocol-related toxicities will not be compared between cohorts.

To compare TDRT and Tumors with LD 50 and LD 70 between two groups, two sample paired t-tests will be conducted when data followed a normal distribution, otherwise Wilcoxon signed rank test will be used instead. General linear model (GLM) will be further used in the multivariable analysis to estimate the adjusted efficacy of treatment (MAA vs Y90) on TDRT and Tumors with LD 50 and LD 70 after adjusting for other factors, respectively. Pearson correlation coefficients will be calculated to measure the correlation between two numerical variables, and the significance of coefficients will be tested using Wald's test.

Time to event outcomes including TTP, PFS and OS will be evaluated using the methods of Kaplan and Meier, with a focus on graphical evaluation as well as early time-point and median estimates of survival distributions with 95% confidence intervals. The TTP, PFS and OS of each patient group at specific time points, such as 1 year, 3 years, and 5 years, etc. were also estimated alone with 95% CI. Cox proportional hazards models were further used in the multivariable analyses to assess adjusted effects of treatment (MAA vs Y90) on the patients' TTP, PFS and OS after

adjusting for other factors. The proportional hazards assumption was evaluated graphically and analytically with regression diagnostics. All data management and statistical analysis were conducted using SAS Version 9.4 (SAS Institute, Inc., Cary, North Carolina).

11. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

11.1 Comprehensive Adverse Events and Potential Risks List

The Adverse Event and Potential Risks list provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Adverse Event List(s) for Y90 Radioembolization with Resin Microsphere [31]:

- Any procedure where the skin is penetrated carries a risk of infection. The chance of infection requiring antibiotic treatment appears to be less than one in 1,000.
- There is a very slight risk of an allergic reaction if contrast material is injected.
- Any procedure that places a catheter inside a blood vessel carries certain risks. These risks include damage to the blood vessel, bruising or bleeding at the puncture site, and infection. The doctor will take precautions to mitigate these risks.
- There is a risk that the microspheres may lodge in the wrong place, putting the patient at risk for an ulcer in the stomach or duodenum. This happens in approximately 2% of patients.
- There is a risk of infection after radioembolization, even if an antibiotic has been given.
- Because angiography is part of the procedure, there is a risk of an allergic reaction to the contrast material.
- **Non-Target Delivery of SIR-Spheres microspheres:** Inadvertent delivery of SIR-Spheres microspheres to extra-hepatic structures such as the esophagus, stomach, duodenum, gallbladder or pancreas may result in radiation injury to these structures. Meticulous angiographic technique must be employed to prevent the non-target delivery of SIRSpheres microspheres to any extra-hepatic structures.
- **Radioembolization Induced Liver Disease (REILD):** Delivery of excessive radiation to the normal liver parenchyma may result in REILD – see description in Section 7. The risk of REILD may also be increased in patients with pre-existing liver disease. Consideration should be given to reducing the prescribed activity of SIRSpheres microspheres in the following clinical settings1 : • Reduced liver functional reserve due to steatosis, steatohepatitis, hepatitis or cirrhosis • Elevated baseline bilirubin level • Small tumor

burden (< 5% liver involvement) • Small liver volume (< 1.5 L) • Prior hepatic resection • Prior liver directed therapy • Extensive prior treatment with systemic chemotherapy and/or biologic therapies.

- **Radiation Pneumonitis:** High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis. The lung radiation dose must be limited to ≤ 30 Gy.

11.2 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

11.3 Definition of Serious Adverse Events (SAE)

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

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

11.4 Classification of an Adverse Event

11.4.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

11.4.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

11.4.3 **Expectedness**

Dr. Kokabi, the PI, and Dr. Schuster, the Co-investigator, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

11.5 Adverse Event and Serious Adverse Event Reporting

11.5.1 Adverse Event Reporting

From the time of treatment allocation through **90** days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.
The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.
Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:
1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials)

Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE

that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.
Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion.

11.5.2 Serious Adverse Event Reporting

For the time period beginning at treatment allocation through **90** days following cessation of treatment, or **180** days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, FDA or Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.
Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

All SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

MedWatch 3500 Reporting Guidelines:
[redacted]
A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Reporting Requirements for IND holder
For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report
The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.
FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.
The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

11.5.3 Reporting to the food and drug administration (FDA)

The Principal Investigator, as holder of the IND (as applicable), will be responsible for all communication with the FDA. The Principal Investigator [or designee] will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.
Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but no later than 7 calendar days after initial receipt of the information.

[redacted]

An annual safety report containing all SAEs, expected and unexpected, will be sent to the FDA and other applicable regulatory authorities.

11.5.4 Expedited reporting requirements for phase 1/2 studies under IND w/in 30 days of last administration of the investigational agent/intervention

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the Sponsoring IRB/FDA within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported to the IRB/FDA within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

11.5.5 Second and secondary malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.**
Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.
A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

11.5.6 Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

12. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

N/A

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

Study participants are responsible for submitting data and/or data forms in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the Associate Director of Clinical Research or the Director of Clinical Trials may temporarily suspend enrollment. Data entry is to be completed within the designated timeframe, not to exceed 30 days of the subject visit.

Queries will be resolved by the research staff within the time frame specified by the protocol, not to exceed 2 weeks.

13.1.1 Source data and documents

In accord with section 1.51 of the ICH E6 document all information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.
Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

Protocol Adherence

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

Retention of Study Documents

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

13.2 Data and Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by

Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

The projected recruitment is 1 patient per week. As such, in order to assure data integrity and protocol adherence, the data will be analyzed every 1 month or after recruitment of 4 new patients. The adverse events will be recorded on an ongoing as dictated by patient follow-up schedule outlines above. As per agreement with SIRTEX, all grades of AE's related to Y90 RE will be recorded based CTACAE guideline. All adverse reactions will also be recorded. Grades 4 and 5 related to Y90 radioembolization will be reported to both Winship DSMC and FDA. All grades of AE's and adverse reactions will be reported to DSMC every 6 months.

The oversight of the study will be performed by Dr. Kokabi and Dr. Schuster during monthly research study meetings with the core study group members. Prior to the meeting, the adherence to protocol and data collection in each individual patient will be confirmed by Dr. Kokabi or Dr. Schuster. The study team members will undergo regular training and review sessions to ensure complete adherence to the protocol. Prior to commencement of the study, all study team

members will undergo mandatory training outlining the protocol and patient recruitment strategies for 2 hours. The study team will then undergo regular monthly research progress meeting to ensure adherence to the protocol and appropriate data collection and reporting.

14. ETHICS AND PROTECTION OF HUMAN SUBJECTS

14.1 Ethical standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, as well as the federal regulations pertaining to ICH E6.

14.2 Institutional review board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

14.3 Informed consent

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

Informed consent is a process that is initiated prior to the individual consent to participate in the study and continues throughout the individual's participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4 Participant and data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

14.5 Research use of stored samples, specimens, or data

Samples and data collected under this protocol may be used to study **HCC.** Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

APPENDIX B ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee

Abbreviation or special term	Explanation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board

Abbreviation or special term	Explanation
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks

Abbreviation or special term	Explanation
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
T_3	Triiodothyronine
T_4	Thyroxine
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization