A Study to Assess the Effect of Y-90 Therapy on Non-target/Background Liver

Protocol Number: RADY-BTG-TANN-HIDA/0603

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1. Background

Liver directed treatment for primary and metastatic tumors has evolved considerably over the past 20 years. There are now several platforms available including bland particles, chemotherapy eluting beads, and radioactive microspheres (Yttrium 90). The toxicity profiles for bland particles and chemotherapy eluting beads are reasonably well studied, and protocols such as super-selective delivery have reduced post procedural liver related complications. The long term liver related complications associated with Yttrium 90 (Y-90) are not well studied, and the variables used to determine eligibility for treatment are inadequate to predict risk of short and long term liver related toxicities.

How Yttrium 90 integrates into current treatment paradigms for primary and secondary cancers will depend on our ability to stratify patients at risk for liver related complications based on relevant functional evaluation of the liver remnant prior to treatment. By assessing global and regional liver function and volume before and after Y-90 therapy, we will be able to determine the potential correlation between Y-90 radiation dose to the background liver and potential radioembolization induced liver damage (REILD). A broader understanding of the relationship between Y-90 and REILD will allow us to develop a safer pre-treatment assessment model for avoidance of and prediction of REILD increasing patient safety and improving Y-90 outcomes.

Measuring liver function is a challenging clinical issue due to its complex microsomal, cytosolic, excretory and synthetic functions.[1] A combination of clinical and laboratory findings are used in daily practice for liver assessment. However, these are not specific or accurate enough to use alone for detection of Y-90 induced regional liver function changes. This is partially due to the liver's unique ability to regenerate after an injury, thereby masking measurable changes. Additionally, laboratory tests only measure by-products of the liver's multiple complex functions. These tests are dependent on substrate availability and volume of its distribution which are unknown and variable and therefore limit their use. Clinical findings also suffer from wide variances in assessment and may be affected by other underlying conditions. If a good measuring tool for liver function were established, we would not need to measure so many lab values, clinical parameters, and clinical findings in addition to using multiple various scoring systems such as MELD and Childs-Pugh.

Quantitative accurate functional testing in general requires administration of a known amount of substrate that the measured function specifically consumes or traps. Two existing techniques that fulfill these criteria for liver function assessment are Indo Cyanine Green clearance (ICG) and a quantitative HIDA scan, a nuclear medicine scan.

ICG clearance is a widely used and validated method for measuring global, but not regional, liver function. Therefore, as both global and regional liver function need to me measured in this study, ICG will not be useful.

The HIDA technique was selected for this study as the gold standard for global and regional liver function. This scan involves administration of a known amount of a specific radiotracer, which is only extracted from the blood pool by the liver. An accurate measurement of liver function can be made by measuring liver and blood pool activity over a set time period using a gamma camera. This technique has been compared to the ICG method and has been found to be similar both in animal and human models.[2,3] It uniquely provides measurement of both global and regional function, and also provides images that can be analyzed unlike the ICG test.

Like any known and used medical test, the HIDA scan has false positives and negatives. However, based on the literature showing good results, we are confident that it is a good choice. Additionally, our preference for HIDA scans is based on our own experience with this technique here at IU. We have been using it here for the past 5 years and have developed and validated specific software, learned how to interpret these studies with confidence, and published on it.[4] It has also shown excellent results for liver surgery planning. Another imaging technique to assess for liver injury is CT scanning. Interval change in organ size can be used as a surrogate for liver radiation injury, with loss of size reflecting degree of damage. However, changes in organ size are much slower to occur and less specific than functional changes as measured by the HIDA scan. As part of routine clinical care, patients undergo multiple scans before and after their Y-90 therapy. We intend to measure global and regional liver volumes through routine CT scans on patients up to 12 months after their therapy to look for slowly occurring changes.

2. Rationale

The primary question of interest is quantifying the relationship between Y-90 liver therapy and liver damage. Little is known on this subject. Present assumptions and calculations of Y-90 administration are based on surgical lobar hepatectomies and external radiation beam therapies. We hope that by using a functional model of the liver, we can improve this important knowledge gap.

We will be enrolling patients planning to receive Y-90 therapy for the treatment of liver malignancies. The diagnosis of a primary liver cancer, hepatocellular carcinoma (HCC), is usually made by a combination of specific imaging findings and clinical criteria; only rarely is a confirmatory biopsy performed. This is due to the high accuracy of the present diagnostic model and the significant risk of biopsy and tumor seeding.

Y-90 therapy involves administering radioactive particles to liver tumors by placing a catheter in a hepatic artery supplying the tumor using angiographic techniques and injection of these particles.

Y-90 PET/CT imaging has been established as a method to validate and quantitate distribution of Yttrium after Y-90 administration. The post Y-90 therapy PET/CT images provide an imaging

distribution of the Y-90, which is essential for validation of administered versus planned dose to the liver lesion and background liver.

If we can compare the Y-90 distribution to estimate background liver radiation distribution and dose (generated by the Y-90 PET/CT scan) combined with the global and regional function map (generated by the HIDA scan performed before and after therapy), then we will be assuming that the difference pre and post therapy in global and regional function can be ascribed to the Y-90 administration. We will also analyze the CT sets performed before and after therapy and correlate the imaging results collected with clinical findings such as ascites/encephalopathy and routine serological markers (bilirubin, albumin, INR, etc.). With this information, we will have the potential to establish whether there is a relationship between Y-90 distribution to non-tumoral (normal) hepatic parenchyma and the incidence and severity of REILD. This would have the potential to improve selection criteria and outcomes in populations selected for Y-90 therapy in the future.

3. Objectives

3.1 Primary Objective:

1. Determine the difference in regional liver function between pre and 3 months post Yttrium 90 delivery using the HIDA functional imaging scans.

3.2 Secondary Objectives:

1. Determine the difference in global liver function between pre and 3 months post Yttrium 90 delivery using the HIDA functional imaging scans.
2. Determine the correlation between the differences in liver function (both regional and global) with the Y 90 dose provided.

4. Eligibility Criteria

4.1 Inclusion Criteria:

1. Subjects must have the ability to understand and the willingness to sign a written informed consent document.
2. Subjects must be ≥ 18 years of age at the time of signing informed consent.
3. Subjects must have a diagnosis of hepatocellular carcinoma (HCC) and a treatment plan to undergo radioembolization therapy with Y-90 at Indiana University Health Hospital.

4. Subjects must be willing and able to comply with all procedures and visits required for this protocol (pre-treatment, during treatment, and post-treatment).

4.2 Exclusion Criteria:

1. Subjects who have contraindications for receiving Y-90 therapy and any routine procedures and imaging associated with Y-90 therapy, including subjects who are pregnant or are planning to become pregnant, will not be eligible to participate in this study. Female subjects who are of childbearing potential should inform her treating physician should she become pregnant at any time during the course of the study.
2. Subjects with contraindications for receiving HIDA scans will not be eligible to participate in this study.

5. Patient Recruitment and Enrollment

Potential subjects will be patients with hepatocellular carcinoma who are planning to undergo Y-90 treatment at Indiana University Hospital. Potential subjects will be recruited through self-referral or the advice of their treating physician or clinical co-investigator on this study.

All patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility. Eligible patients who complete the Informed Consent Process will be assigned a unique subject ID number and enrolled as a subject to this study. The subject will be given a copy of the signed, IRB-approved informed consent and HIPAA authorization documents, and the original signed informed consent and HIPAA authorization documents and regulatory files will be maintained by the Radiology Research Office. The process of obtaining consent (including date) must be clearly documented in the source documentation for this study. Applicable regulatory documents and approvals must be completed and on file prior to the enrollment of any subjects.

Subjects will be compensated for their time and effort with a $25.00 gift card upon completion of each research imaging scan. A potential total of $50.00 disbursed in gift cards per subject by the end of their participation in the study, if they undergo and complete the pre-Y90 HIDA and post-Y90 HIDA scan.

6. Study Procedures

6.1 Screening

Screening procedures to determine eligibility will include obtaining demographics and relevant medical history.

6.2 Pre Y-90 therapy

Each subject will undergo a HIDA scan after enrollment but prior to the initiation of Y-90 therapy for the purposes of this study. Additional imaging and laboratory tests will also be as part of routine clinical care prior to Y-90 therapy. These tests are the Tc99m MAA scan, CT scan, MELD/BCLC assessment and a blood serum chemistry test. The results of these tests will be collected for this study.

A HIDA scan involves the intravenous administration of a small amount of a radioactive tracer and imaging of the liver using a SPECT gamma camera. A 5 Mci dose of radioactive tracer mebrofenin **(**Tc99m bromo-2,4,6-trimethylacetanilido iminodiacetic acid) (HIDA) will be administered while the patient is on the imaging table. Images of the liver will be acquired for 30 minutes.

Whenever possible, the HIDA scan will be performed on the same day as the routine CT scan in order to use the intravenous access already placed for the CT imaging and minimize patient discomfort.

Adverse events will be assessed anytime procedures are being performed for research purposes only (i.e., HIDA).

6.3 Post Y-90 therapy

- At the time of Y-90 therapy, subjects will undergo a PET-CT scan to measure Yttrium distribution post-delivery of Y-90 per routine clinical practice.
- 3 months - Each subject will undergo a second HIDA scan approximately 3 months (+/- 30 days) after Y-90 therapy for the purposes of this study. Adverse event assessment will also be performed. Subjects will also have a CT scan and blood serum chemistry test as part of their routine clinical follow-up approximately 3 months (+/- 30 days) after Y-90 therapy, and the results of these tests will be collected for this study.
- 6 and 12 months - Subjects will have a CT scan and blood serum chemistry test as part of their routine clinical follow-up approximately 6 and 12 months (+/- 30 days) after Y-90 therapy, and the results of these tests will be collected for this study.

7. Study Calendar

	Pre Y-90 therapy		Y-90 Therapy	Post Y-90 Therapy		
	Screening	**After enrollment but prior to Y-90 therapy**		**3 months**	**6 months**	**12 months**
	Within 28 days of Y-90 therapy			+/- 30 days	+/- 30 days	+/- 30 days
	Administration					
Informed consent	X					
Demographics	X					
Medical history	X					
Enrollment	X					
Adverse events assessment		X		X		
MELD/BCLC	X[3]					
	Routine Labs and Imaging Procedures					
Blood serum chemistry		X		X	X	X
Tc99m MAA scan		X				
CT scan		X		X	X	X
PET-CT			X[2]			
	Research Labs and Procedures					
HIDA scan[1]		X		X		

Footnotes:
[1]Whenever possible, the HIDA scan will be performed on the same day as the standard of care CT scan in order to use the intravenous access already placed for the CT imaging to minimize patient discomfort.
[2]At the time of Y-90 therapy, subjects will undergo a PET-CT scan to measure Yttrium distribution post Y-90 delivery per routine clinical practice.
[3] MELD/BCLC will be collected per standard of care

8. Potential Risks and Procedures for Minimizing Risks

8.1 Risks Involved in a Hepatobiliary (HIDA) Scan

The risks involved in a HIDA scan are minimal. They include the following:

1. Radiation exposure; a very small amount of radioactive material is used and the radiation exposure is well below the level that causes adverse effects.
2. Allergic reactions to the radioactive material; however, this is extremely rare and without documented cases.

3. Discomfort, bruising or rash at the injection site or discomfort while lying on the table for the required amount of time for the scan. An effort will be made to schedule the HIDA scan at the same time as routine CT imaging in order to minimize discomfort.

8.2 Risks with Radiation

A very small amount of radioactive material is administered for the HIDA scan; therefore, subjects enrolled in this study will be exposed to radiation in addition to what is received as part of standard of care. The additional radiation exposure is well below the level that would cause adverse events. Please see table below for details regarding additional radiation exposure.

Administered Activity vs Dose Table:

	Administered activity		Largest radiation dose			Effective dose	
Radiopharmaceutical	MBq	mCi	Organ	mGy/MBq	rad/mCi	mSv/MBq	rem/mCi
^{99m}Tc-disofenin or ^{99m}Tc-mebrofenin	56–180 intravenously	1.5–5.0	Gallbladder wall	0.11	0.41	0.017	0.063

9. Potential Benefits

There will be no direct benefit to the patients participating in this study; however, one potential benefit of the study is the potential contribution to a greater understanding of the mechanisms of liver functioning and safety in radioembolization therapy with Y-90 for hepatocellular carcinoma.

10. Criteria for Removal from Study

Every subject should be encouraged to remain in the study. Possible reasons for early withdrawal may include, but are not limited to, the following:

1. Withdrawal of consent – Subject decides to withdraw from the study. This decision must be an “independent decision” that is documented in the source documentation.
2. Principal Investigator and/or treating physician discretion – The Principal Investigator and/or treating physician may choose to withdraw a subject from the study if there are safety or other concerns.
3. Subject’s treatment plan for Y-90 therapy is cancelled.

4. Subject's treatment location for Y-90 therapy is moved to another institution outside of Indiana University Health Hospital.
5. Subject becomes pregnant.
6. Subject has contraindication to HIDA scan that is discovered after enrollment.
7. Subject non-compliance.
8. Subject lost to follow-up.
9. Subject death.

11. Statistical Considerations

11.1 Design

This is a single-institution, non-randomized pilot study to assess the potential of using additional nuclear medicine scans to assess risk of liver related complications after Y-90 therapy.

We plan to enroll 50 patients with hepatocellular carcinoma who are planning to receive Y-90 therapy at Indiana University Health Hospital. Enrollment for this study is expected to last 18 months. Data analysis expected to be completed approximately one year after the last subject's 12-month follow-up data is collected. The duration of individual subject participation will be approximately 12 months.

11.2 Sample Size

It is not easy to preliminarily and definitively assess whether 50 patients will be sufficient to achieve meaningful comparisons and correlation calculation in all subgroup goals. However, after reviewing many pre and post Y-90 liver studies over the past years as well as current literature, there is always decrease in surrounding regional peri-tumoral liver volumes related to this therapy/radiation damage. Therefore, each case will have some component of liver damage, the majority subclinical, which can be captured with global and regional liver volume (CT scan) and functional HIDA scan assessment. Additionally, current literature suggests that there will be a 19% incidence of clinically significant radiation induced liver disease. This will be revealed by abnormal laboratory studies and specific symptoms which have already been classified in current literature as well as global and regional changes in liver function and volume as assessed by the HIDA and CT scans.[6]

When the sample size is 50, a two-sided 95% confidence interval for an expected proportion of 19% will extend 10.9% from the observed proportion using the large sample normal approximation. Therefore, with 50 patients we expect to have 50 cases of some component of Y-90 therapy induced liver damage, largely subclinical and approximately 10 clinical cases.

11.3 Analysis

Regional HIDA scan clearance rate results will be used for the primary analysis of the difference in regional liver failure between pre and 3 months post Y90 administration. Paired t-tests will be used. A similar method will be used for the global liver function difference. If the data is found to not be normally distributed, appropriate non-parametric tests will be performed for the comparisons. Spearman's correlation will be used to correlate the Y90 dose with the difference in regional and global liver function

12. Reporting Adverse Events

12.1 Definitions of Adverse Events

12.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient, not necessarily having a causal relationship with the study. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the study, whether or not related to the study.

12.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

1) Results in death or ANY death occurring within 28 days of date of study intervention (even if it is not felt to be study related)
2) Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3) Requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization
    - **NOTE**: Hospitalizations that are not considered SAEs are:
        - Hospitalization planned prior to first study intervention
        - Hospitalization less than 24 hours
        - Hospitalization for elective treatment of a pre-existing condition unrelated to the study intervention
4) Results in persistent or significant disability/incapacity
5) Is a congenital anomaly or birth defect
6) Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical

and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

12.1.3 Unexpected Adverse Event

An adverse event not associated as a known risk or adverse event.

12.1.4 Determining Attribution to the Investigational Procedure

Attribution: An assessment of the relationship between the AE and the study intervention. CTCAE does not define an AE as necessarily "caused by a therapeutic intervention". After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	**Attribution**	**Description**
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

12.2 Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

The Institution and the Sponsor-Investigator shall, in accordance with ICH GCP guidelines and all applicable Federation Regulations, report all and any adverse events in relation to the Product and/or the investigation to the relevant authority or authorities as shall be required by the listed applicable Laws and regulations. BTG is not responsible for safety reporting of adverse events identified during this study.

The Sponsor-Investigator shall report to BTG all device malfunctions/quality complaints within 1 business day to quality@biocompatibles.com. The Sponsor-Investigator shall report to BTG Pharmacovigilance all adverse events regardless of seriousness or causality between the adverse events and the BTG product by the 17th of each month. The report will list all adverse events, along with comprehensive event narratives and will reference the study title, the BTG study reference number and the name of the Sponsor-Investigator.

The Institution and the Sponsor-Investigator will also provide BTG with such information and reasonable assistance as may be requested by BTG to allow BTG to comply with their obligations. All AE or safety related correspondence with BTG should be addressed to pharmacovigilance@btgplc.com.

Only adverse events occurring during the HIDA research scan will be captured for this study. Should they occur, adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0. See Section 17.0 for reporting requirements

All AEs considered related to the HIDA scan will be followed until resolution, return to baseline, or deemed clinically insignificant.. Any death occurring within 30 days after the last study intervention must be reported as an SAE regardless of attribution.

12.2.1 Reporting to the IRB:

1. Unanticipated problems involving risks to subjects or others will be reported promptly to the IRB if they:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review

2. Prompt reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

12.2.2 Reporting to the Data Safety Monitoring Committee (DSMC):

Regardless of study sponsorship, this study is subject to monitoring by the Indiana University Simon Cancer Center Data Safety Monitoring Committee (DSMC). The DSMC chair and/or coordinator will review all expedited SAE reports through OnCore®. Expedited reports are completed per IRB guidelines and may include the IRB prompt reporting form, non-compliance form, AdEERS reports, MedWatch, and additional SAE forms as required by the sponsor. Submission of this information to the DSMC is additional to any other protocol-specified regulatory bodies (e.g., FDA, pharmaceutical company) to be notified. When follow-up information is received, a follow-up report should also be created in OnCore®. The DSMC chair and/or coordinator will review expedited SAE reports monthly and report findings to the DSMC quarterly.

13. Patient Consent and Peer Judgment

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the Principal Investigator and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

14. Privacy/Confidentiality

At the time of enrollment, subject protected health information (PHI) will be limited to that considered essential to meeting the study goals. Non-essential subject identifiers, such as date of birth, or other identifying information will be secured within the database. The PI and his designees will ensure PHI collected for this study is secured in compliance with institutional and legal requirements. All data will be maintained in a locked non-public area. Computer files will be password protected and paper records stored in a lockable file cabinet.

Subject confidentiality will be maintained throughout the study by use of a unique subject identification code that allows blinded identification of all data reported for each subject. The site will maintain a Master Subject Log that will be the only source linking the subject ID to the subject's identifiable information. This will be maintained by the PI and/or his designees in a secure location with limited access.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the subject's privacy is guaranteed.

15. Data Forms and Submission Schedule

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore® at https://cancer.iu.edu/oncore.

Summary accrual information, protocol deviations, and serious adverse events will be reported in OnCore per IUSCC guidelines.

OnCore® is developed by Forte Research Systems, Inc. (www.forteresearch.com). OnCore® Enterprise Research is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. It has been licensed by Indiana University (IU) used by the IUSCC Clinical Trial Office (CTO) and supported by the Indiana Clinical and Translational Sciences Institute (CTSI) to support the operations and data capture of clinical research trials.

Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user that limits access to appropriate data.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines.

All CRFs and all source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses, procedure dates, and investigational product disposition records) that support the CRFs must be retained in the files of the Principal Investigator for a minimum of three years following notification that all investigations have been terminated or completed. This documentation must be accessible upon request by the FDA or Sponsor.

16. Data Safety Monitoring Plan

Investigators will conduct continuous review of data and patient safety. Quarterly review meetings for low risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Quarterly meeting summaries should include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Summaries will be submitted quarterly and reviewed by the DSMC for review. Submit to DSMC@iupui.edu.

16.1 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing/monitoring. Reports will be forwarded to the DSMC for review.

16.2 Early Study Closure

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review of the investigator reports.

16.3 Reporting Guidelines

The DSMC has streamlined the reporting process by utilizing reports from OnCore. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore and reviewed by the DSMC chair and/or coordinator monthly.

16.4 Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

16.5 Protocol Deviations

Protocol deviations are entered into OnCore and reviewed by the DSMC chair and/or coordinator monthly.

17. References

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