Cover Page

Study Title:

Yttrium-90 Radioembolization for Cirrhosis-Associated Thrombocytopenia

NCT:

NCT03059030

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Protocol version 25 dated 5.7.2020

STUDY SUMMARY

Title **Yttrium-90 Radioembolization for Cirrhosis-Associated Thrombocytopenia**

Short Title 90Y for Thrombocytopenia

Protocol Number G160096 v. 25 dated 5/7/2020

Phase Pilot study

Methodology Open labeled, non-randomized feasibility study

Study Duration We estimate it will take approximately 6 years or 72 months to fully enroll and complete the study.

Study Center(s) Single Center, Northwestern: (Northwestern University, Northwestern Memorial Hospital)

Objectives Primary Objective: Evaluate the safety and efficacy of 90Y radioembolization for the management of thrombocytopenia.

Number of Subjects 20

Diagnosis and Main Inclusion Criteria Subjects with thrombocytopenia secondary to cirrhosis

Study Product(s) TheraSphere® Yttrium-90 Glass Microspheres, BTG International Inc.

Duration of administration Dose administered by Interventional Radiologist

Statistical Methodology Descriptive statistics will be employed.

STUDY OBJECTIVES

2.1 Primary Objectives

Endpoint #1: Patient safety

The Primary Objective of this pilot study is to evaluate the safety of 90Y RE for the treatment of thrombocytopenia in the setting of cirrhosis. Primary Safety Endpoints include:

1. Assess safety of splenic administration of 90Y. [i.e. the onset of AEs such as infection or abscess as assessed by NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0.3.)]

2. Assess the utility of splenic 99mTc-MAA injection to determine shunting prior to 90Y RE.

3. Assessment of short-term and long-term post-procedure events

Endpoint #2: Objective clinical endpoints

1. To achieve a 50% increase in platelet count six months after therapy. This will be assessed via CBC with differential at all study visits.

2. To achieve a 20% decrease in functional splenic volume six months after treatment. This will be assessed via cross-sectional CT or MR of the abdomen at screening and at 4 weeks, three months, and six months after 90Y infusion.

2.2 Secondary Objectives

1. For patients who are hospitalized after RE, to determine the average length of stay after treatment.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

Inclusion Criteria

Patients must meet the following eligibility criteria at entry:

3.1.1. Male or female, 18 years of age or older, of any ethnic or racial group.

3.1.2. Diagnosis of cirrhosis or portal hypertension with a serum platelet count less than or equal to 80 × 109/L, but no less than 10 × 109/L . [Rationale: platelet count <100 × 109/L triples the rate of liver- related adverse events (3) and worsens postoperative survival in the setting of HCC (4). Initial platelet count of 80 × 109/L can allow the majority of patients who successfully respond to 90Y-RE (clinical endpoint of 50% platelet count increase) to exceed the 100 × 109/L threshold.]

Cirrhosis is defined by one of three criteria:

3.1.2.1. Liver Biopsy/histology consistent with cirrhotic architectural liver changes

3.1.2.2. Portal hypertension (Hepatic venous pressure gradient ≥10 mm Hg)

3.1.2.3. Evidence of esophageal and/or gastric varices

3.1.3. Patients must have evidence of splenomegaly as determined by Screening crosssectional

imaging.

3.1.4. No evidence of myelosuppression (e.g. lymphopenia) as evidenced by normal hematology values at screening (except in cirrhotic patients).

3.1.5. Adequate baseline organ function as evidenced by normal BUN/Cr and electrolytes on screening chemistry (except in cirrhotic patients).

3.1.6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-2

3.1.7. Patient has a life expectancy of greater than 6 months without intervention.

3.1.8. Patient is willing to participate in the study and has signed the study informed consent.

3.1.9. Women of childbearing potential must have a negative serum pregnancy test within 28 days prior to screening and must not be breastfeeding.

3.2 Exclusion Criteria

3.2.1. Patients with serum platelet count less than 10 × 109/L.

3.2.2. History of bleeding disorder attributed to another cause other than cirrhosis (e.g. von Willebrand disease)

3.2.3. Declines or unable to provide informed consent

3.2.4. History of prior PSE or splenectomy

3.2.5. Use of any medication known to increase platelet count 1 month prior to Baseline.

3.2.6. History of allergy or sensitivity to TheraSphere® or its components.

3.2.7. History of severe peripheral allergy or intolerance to contrast agents, narcotics, sedatives or atropine that cannot be managed medically

3.2.8. Contraindications to angiography and selective visceral catheterization such as bleeding, diathesis or coagulopathy that is not correctable by usual therapy or hemostatic agents (e.g. closure device)

3.2.9. Previous randomization in a trial using 90Y RE

3.2.10. Patient must not have participated or enrolled in a clinical trial with an investigational device / therapy within 30 days prior to randomization

3.2.11. Any serious medical condition likely to impede successful completion of the study, such as certain mental disorders, cardiac arrhythmias, and uncontrolled

congestive heart failure or respiratory disease.

3.2.12. Patients actively on chemotherapy.

STATISTICAL CONSIDERATIONS

All patients will be accounted for in the final analysis. All patients who discontinue or withdraw after enrollment and before reaching the final follow-up period will be summarized by their reason for discontinuation/withdrawal and will contribute to the analyses as described below and in the statistical analysis plan.

Since this is an exploratory point of care study, the 20 patients are being used to look for a signal. Thus, a Simon's statistical design will not be utilized.

12.1 Trial Design and Objectives

This is an open label, prospective, single-center trial assessing the safety and efficacy of TheraSphere® delivered to the spleen for the treatment of cirrhosis-associated thrombocytopenia. The primary objectives of this trial are to determine the safety of splenic 90Y delivery with TheraSphere®, the improvement in blood platelet count, and reduction in splenic volume.

12.2 Sample Size Determination

As a proof-of-pilot study, the primary rationale is safety. Once the patients are studied, secondary hypotheses may be generated to better refine patient selection and clinical applicability. Though missing data points may occur, statistical analysis will be conducted with the available acquired information.

12.3 Demographics

Descriptive statistics of demographics, medical history, disease severity, time from diagnosis, physical exam, and other baseline characteristics will be presented for all patients.

Efficacy

Descriptive statistical analyses will be used for the safety and efficacy.

12.5 Safety and Outcome Analysis

Clinical and outcome measures will be compared to baseline. These include platelet count and splenic volume.

Safety measures will be monitored at each study visit. These include the adverse event reporting;

physical examination; and cross-sectional imaging to assess for radio-pathologic findings. MAA will be conducted for the first four patients. The lung shunt study data will be provided to the FDA for review when all 4 patients have completed the lung shunt study before the 5th patient is scheduled for 90Y therapy. If average shunt of first four patients is less than 5%, then all subsequently enrolled patients will not undergo MAA. If average shunt is >5%, the next 6 patients will undergo MAA. If the average shunt among the 10 patients is >5%, then all subsequent patients will undergo MAA. Otherwise, the remaining patients will not receive MAA.

In addition to the conventional angiogram, we will perform 3-dimensional rotational angiography/cone beam computerized tomography in all patients. Conventional angiography and cone beam CT essentially eliminate the chance of aberrant deposition of the radioactive microspheres. Subjects who do not undergo pretreatment MAA will undergo post-treatment 90Y PET scan.

Interim Analysis

An interim analysis will be performed after the 10th patient is enrolled. It will include patient registration, treatment and follow-up information including any adverse events and any concomitant medications which were taken due to study treatment and/or procedures per treating investigator. It will summarize the results of the primary and secondary objective clinical endpoints. Any protocol deviations will be listed as well.

STATISTICAL ANALYSIS

14.1 General Considerations

General considerations: continuous variables will be summarized as n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized as the number and percentage of patients in each category.

14.2 Sample Size Accrual

This is a single center pilot study aiming to evaluate the safety, efficacy, and tolerability of 90Y RE for cirrhosis-associated thrombocytopenia. A small number of subjects will be recruited for this purpose (20 subjects). The first 4 subjects will receive planning angiography and MAA. They will be carefully monitored for adverse events to establish preliminary safety of initial dosing plan. The lung shunt study data will be provided to the FDA for review when all 4 patients have completed

the lung shunt study before the 5th patient is scheduled for 90Y therapy. We estimate it will take approximately 6 years to recruit, treat, and complete follow up on 20 subjects. The results of the study will provide critical preliminary data to later guide in powering a more statistically robust, and larger randomized controlled trial in the future.

14.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics must include age, gender, race, ethnicity, concomitant medications, prior therapy, past medical history, and prior surgical history. Ancillary information can be noted by the clinical coordinator as appropriate.

14.4 Safety and Outcome Analysis

Clinical and outcome measures will be compared to baseline.

14.5 Duration of Procedure

Parameters to be recorded include during of procedure, number of TheraSphere® vials used, radiation exposure, catheter/wire used and amount of contrast.

14.6 Laboratory evaluations

Summary statistics for baseline and change from baseline will be summarized.

14.7 Vital signs

Summary statistics for baseline and change from baseline will be summarized.

14.8 Imaging

Imaging results will be summarized for baseline and all subsequent imaging**.**