NRG ONCOLOGY

NRG-GI003

(ClinicalTrials.gov NCT #: 03186898)

A Phase III Randomized Trial of Protons Versus Photons for Hepatocellular Carcinoma

Amendment 4: December 19, 2025

NRG ONCOLOGY
NRG-GI003
(ClinicalTrials.gov NCT #03186898)(30-July-2018)

A PHASE III RANDOMIZED TRIAL OF PROTONS VERSUS PHOTONS FOR HEPATOCELLULAR CARCINOMA

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

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A PHASE III RANDOMIZED TRIAL OF PROTONS VERSUS PHOTONS FOR HEPATOCELLULAR CARCINOMA

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Document History

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This protocol was designed and developed by NRG Oncology. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by NRG Oncology nor does NRG Oncology assume any responsibility for unauthorized use of this protocol.

The following NCTN Group Study Champions have been added to this trial:
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CONTACT INFORMATION (19-DEC-2025)

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org).

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
For imaging data submission questions: IROCimagearchive@acr.org; please include trial number in the email subject line **For TRIAD access and installation support:** TRIAD-Support@acr.org Triadhelp.acr.org **TRIAD Software Installation:** https://triadinstall.acr.org/triadclient/

TABLE OF CONTENTS

SCHEMA **9**

1. OBJECTIVES **10**
1.1 Primary Objective 10
1.2 Secondary Objectives 10
1.3 Exploratory Objectives 10

2. BACKGROUND **10**
2.1 Rationale for selected approach and trial design. 10

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA **12**
3.1 Patient Selection Guidelines 12
3.2 Eligibility Criteria 13
3.3 Ineligibility Criteria 14

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP **15**

5. TREATMENT PLAN/REGIMEN DESCRIPTION **17**
5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy 17
5.2 Radiation Therapy 17
5.3 General Concomitant Medication and Supportive Care Guidelines 32
5.4 Duration of Therapy 33

6. TREATMENT MODIFICATIONS/MANAGEMENT **33**

7. ADVERSE EVENTS REPORTING REQUIREMENTS **34**
7.1 Protocol Agents 34
7.2 Adverse Events and Serious Adverse Events 34
7.3 Expedited Reporting of Serious Adverse Events 35
7.4 Reporting to the Site IRB/REB 36
7.5 Secondary Malignancy 36
7.6 Routine Reporting Requirements for Adverse Events 37

8. REGISTRATION, STUDY ENTRY PROCEDURES **37**
8.1 Cancer Trials Support Unit Registration Procedures 38
8.2 Letter of Intent –ALL SITES 41
8.3 RT-Specific Pre-Registration Requirements 41
8.4 Digital Radiation Therapy Data Submission Using Transfer of Images, and Data 42
8.5 Patient Enrollment 43

9.0 DRUG INFORMATION **44**

10.0 PATHOLOGY/BIOSPECIMEN **44**
10.1 Biospecimen Submission Tables 44

10.2 Tissue Selection for Integrated marker testing: 45
10.3 Location of testing 48
10.4 Tissue Submission for testing: See Biospecimen Submission tables below....48

11.0 SPECIAL STUDIES (NON-TISSUE) 50
11.1 Patient Reported Outcomes (PROs)....50
11.2 Quality-Adjusted Survival 52
11.3 Imaging Component....53

12.0 MODALITY REVIEWS 54
12.1 Radiation Therapy Quality Assurance Reviews 54

13.0 ASSESSMENT OF EFFECT 55

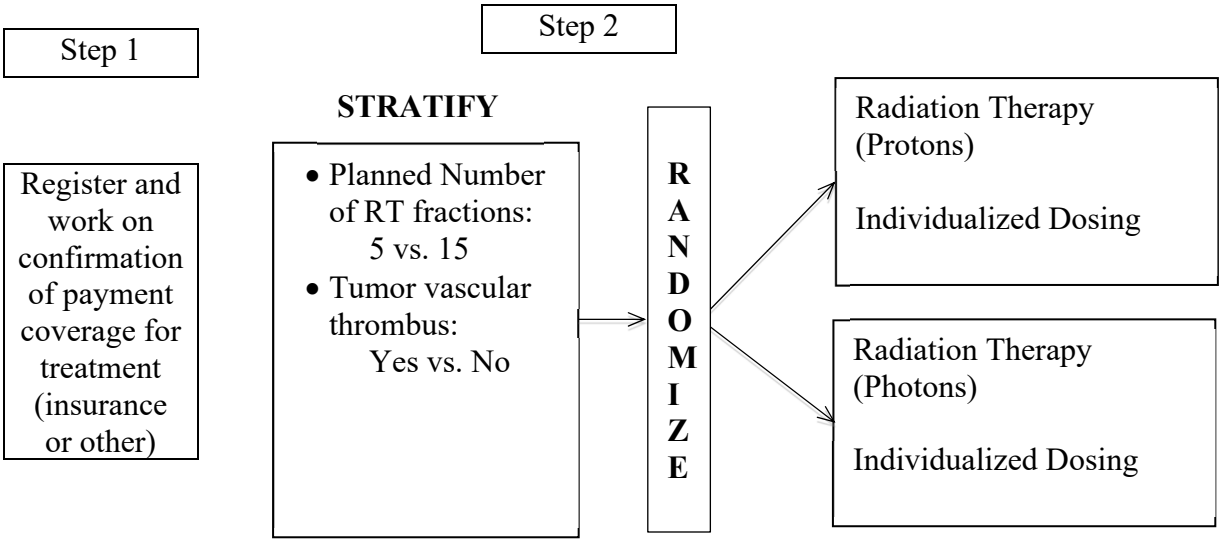
14.0 DATA AND RECORDS 55
14.1 Data Management/Collection 55
14.2 Summary of Data Submission 56
14.3 Data Quality Portal 59
14.4 Global Reporting/Monitoring 60

15.0 STATISTICAL CONSIDERATIONS 60
15.1 Study Design....60
15.2 Study Endpoints....60
15.3 Primary Objectives Study Design....60
15.4 Secondary/Exploratory Endpoints 63
15.5 Translational Research....66
15.6 Other Pre-specified Outcomes: NIH Required Analyses for Trials with Phase III Components....67
15.7 Sex/Ethnicity/Race Distribution 67

REFERENCES....69

APPENDIX I 72

NRG-GI003
SCHEMA



1. OBJECTIVES

1.1 Primary Objective

To determine if overall survival (OS) is different for hepatocellular carcinoma patients treated with protons compared to photons.

1.2 Secondary Objectives (18-OCT-2019)

1.2.1 To determine the difference in progression-free-survival (PFS) in patients with HCC treated with protons compared to patients with HCC treated with photons.

1.2.2 To determine the difference in local progression (LP) in patients with HCC treated with protons compared to patients with HCC treated with photons.

1.2.3 To determine differences in toxicity in patients with HCC treated with protons versus photons.

1.2.4 To determine differences in fatigue, as measured by PROMIS Fatigue in patients with HCC treated with protons, versus photons; as well as quality-adjusted survival if the primary endpoint is met.

1.2.5 To determine if there are correlations between the baseline values of hepatocyte growth factor (HGF) and outcomes (OS/PFS/fatigue).

1.3 Exploratory Objectives

1.3.1 To determine differences in overall Quality of Life, measured by FACT-Hep in patients with HCC treated with protons.

1.3.2 Biospecimen collection for future correlative science projects.

2. BACKGROUND

2.1 Rationale for selected approach and trial design.

Radiation therapy has emerged as a therapeutic option for hepatic confined HCC. The delivery of therapeutic doses of radiation for liver tumors was made possible by the use of cross-sectional imaging, improved dose delivery techniques, and respiratory management strategies. The commonly used radiation for HCC is photon-based given in 3-6 fractions, also known as stereotactic body radiation therapy (SBRT). The largest prospective report of SBRT is a phase I and II Toronto SBRT studies of 102 Child-Pugh A HCC patients ineligible for local-regional therapies (38% Hepatitis B, 38% Hepatitis C, 25% alcohol; 55% portal vein thrombosis; 12% extrahepatic disease) treated with SBRT in 6 fractions (median dose 36 Gy in 6 fractions) from 2004 to July 2010 found a median survival of 17.0 months. Radiation dose was based on the dose that the uninvolved liver received, to maintain a low risk of radiation induced liver disease (RILD). A dose response for local control was observed (Bujold 2013), with tumors receiving >30 Gy showing improved local control.

Proton therapy is a form of external beam radiation therapy that utilizes accelerated protons as particles to deliver therapeutic radiation. The benefit of protons derives from the lack of exit dose, as the depth of penetration and energy deposition of protons is related to the velocity at which the protons are emitted. Theoretically, when using a dosing schema utilizing mean liver dose, the lack of exit dose may allow for a potentially greater dose of radiation delivered to the tumor.

Protons remain a controversial modality due to cost and an unproven benefit in overall survival. However, in aggregate, single arm studies suggest superior results compared with photon studies. This randomized trial seeks to directly answer if protons are superior to photons.

We have recently completed a phase II study evaluating a 15 fraction schedule (DF/HCC). Patients with HCC with Child's A/B, ECOG PS 0-2, no extrahepatic disease, no prior RT were eligible (Hong 2015). Maximum tumor size was 12 cm if solitary, 10 cm if 2 tumors, and 6 cm if 3. Proton therapy was given in 15 fractions to a maximum total dose of 67.5 GyE. 49 patients with HCC were enrolled. With a median follow up of 22.1 months in survivors, 1- and 2- year incidence of local recurrence was 5%. Median survival was not reached, with a Kaplan-Meier estimate of 2-year survival of 71%. In contrast, the above mentioned Princess Margaret Hospital (PMH) prospective trial (Bujold 2013) with SBRT for HCC that forms the foundation for the ongoing RTOG study, reported a LC-2 of <80% (estimated) and a 2-year OS of 34%. The difference in the results of the current study and PMH report should be interpreted with caution and cannot be specifically attributed to the modality of protons vs. photons. First, PMH accrued a higher risk group of patients, with a larger median tumor size and volume, a greater percentage of patients with a Cancer of the Liver Italian Program (CLIP) score > 2, and a greater percentage of patients of patients with tumor vascular thrombus (TVT). Second, the current study, as well as the other proton studies, used a hypofractionated regimen of 15 fractions, rather than the six fraction schedule used in the PMH study. Recognizing the limitations of the linear-quadratic model to compare fractionation schedules, it is interesting to note that the highest allowed doses (67.5 GyE/15 fractions or 54 Gy/6 fractions) in these two studies are quite similar in 2-Gy equivalent dose (82 Gy vs. 86 Gy respectively) for tumor effect ($\alpha/\beta=10$). However, the median doses in the current study (58 Gy/15 fractions) vs. the PMH study (36 Gy/6 fractions) are quite different in 2 Gy-equivalents (67 Gy vs. 48 Gy, respectively). Thus, part of the difference in local control may also be related to the fractionation schedule used.

However, another contribution to the difference in overall survival between the current series and PMH may be the impact of protons versus photons on post-treatment hepatic function. Only 3.6% of patients in the overall cohort in the current study had any decrease in CTP (Child-Turcotte-Pugh) class. This compares favorably to the 29% of patients with worsening CTP class at 3 months reported in the PMH study. Worsening CTP class has been associated with a significant decrease in survival (Son 2014) The individualized dosing strategy based on MLD is designed to maintain a low risk of classic radiation induced liver disease (RILD), a veno-occlusive syndrome, rather than to preserve long-term hepatic function. However, it remains unknown if higher MLD that is below a threshold RILD risk is associated with a risk of worsening in CTP class. Again, using the linear-quadratic model to account for fractionation differences, the average MLD (in 2-Gy equivalents, $\alpha/\beta=3$) for HCC patients in this series was lower than in the PMH series (9.6 Gy vs. 18.0 Gy). Prior efforts to characterize dose-volume parameters predicting worsening CTP class, as opposed to RILD are limited, with one study suggesting that sparing 800 mL of liver from a conventionally fractioned dose equivalent of 30 Gy was the key parameter (Son 2010). Therefore, the rationale for this study is to

compare proton versus photon therapy in the treatment of hepatocellular carcinoma with an overall survival endpoint.

The largest prospective report of SBRT for HCC is a phase I and II Toronto SBRT studies (Bujold 2013) of 102 Child-Pugh A HCC patients ineligible for local-regional therapies (38% Hepatitis B, 38% Hepatitis C, 25% alcohol; 55% portal vein thrombosis; 12% extrahepatic disease) treated with SBRT in 6 fractions (median dose 36 Gy in 6 fractions) from 2004 to July 2010 found a median survival of 17.0 months. Radiation dose was based on the dose that the uninvolved liver received, to maintain a low risk of radiation induced liver disease (RILD).

Massachusetts General Hospital (MGH)/MD Anderson Cancer Center (MDACC)/ University of Pennsylvania (UPenn) reported a phase II study evaluating a 15 fraction schedule (DF/HCC). Patients with HCC with Child's A/B, ECOG PS 0-2, no extrahepatic disease, no prior RT were eligible (Hong, 2015). Maximum tumor size was 12 cm if solitary, 10 cm if 2 tumors, and 6 cm if 3. Proton therapy was given in 15 fractions to a maximum total dose of 67.5 GyE. 49 patients with HCC were enrolled. With a median follow up of 22.1 months in survivors, 1- and 2- year incidence of local recurrence was 5%. Median survival was not reached, with a Kaplan-Meier estimate of 2-year survival of 71%. The discrepancy in survival between the two studies may be explained by difference dosing due to protons, or a lack of radiation dose to the uninvolved liver with protons. Alternatively, the difference in OS may be related to patient selection. These discrepant results provide the rationale for the randomized trial of protons vs. photons.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active must be willing and able to use medically acceptable forms of contraception during the radiation therapy.

3.1.3 Submission of blood and tumor tissue (if available) is requested for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See details of submissions in Section 10.)

3.2 Eligibility Criteria (30-July-2018)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to STEP ONE Registration

3.2.1 Pathologically (histologically or cytologically) or radiographically-proven (based on the American Association for the Study of Liver Diseases [AALSD] criteria) unresectable or locally recurrent hepatocellular cancer prior to registration;

3.2.2 Appropriate stage for study entry based on the following diagnostic workup:

- All patients must have CT scan chest/abdomen/pelvis with multiphasic liver CT scan prior to registration. If CT contrast is contraindicated, CT chest without contrast and MRI of abdomen is permitted.
- Participants must have measurable disease at study entry, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >2 cm with conventional techniques or as >1 cm with spiral CT scan.
- Patient must have 3 or fewer single or multinodular tumors. For patients with a single lesion, lesion must be 15 cm or less in greatest dimension. For patients with two lesions, no lesion may be greater than 10 cm in greatest dimension. For patients with three lesions, no lesion may be greater than 6 cm in greatest dimension. Portal vein involvement or thrombosis combined with a single lesion that is ≥ 1 cm and ≤ 15 cm in greatest dimension is allowed.

3.2.3 Age ≥ 18

3.2.4 Zubrod Performance Status 0-1 within 30 days prior to registration;

3.2.5 Negative urine or serum pregnancy test for women of childbearing potential within 7 days prior to study entry;

3.2.6 Adequate hematologic function prior to registration defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3;
- Platelets ≥ 50,000 cells/mm^3;
- Hemoglobin ≥ 9.0 g/dl. (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable.)

3.2.7 Adequate renal/hepatic function prior to registration defined as follows:

- Total bilirubin < 4 x institutional upper limit of normal (ULN);
- Transaminases (AST and ALT) < 6 x institutional ULN;
- Albumin ≥ 2.5 g/dl;
- Creatinine < 2 mg/dl.

3.2.8 Prior chemotherapy, targeted biological therapy (e.g. sorafenib), surgery, transarterial chemoembolization (TACE), ablation for present disease is acceptable.

3.2.9 Must have Child-Turcotte-Pugh (CTP) A or B7

3.2.10 The patient or a legally authorized representative must provide study-specific informed consent prior to study registration.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

Prior to STEP ONE Registration

3.3.1 Definitive clinical or radiologic documentation of extrahepatic tumor, defined as extrahepatic metastases or malignant nodes (that enhance with typical features of HCC) > 3.0 cm, in sum of maximal diameters (e.g. presence of one 3.4 cm metastatic lymph node or two 2 cm lung lesions). Note that benign non-enhancing periportal lymphadenopathy is not unusual in the presence of hepatitis and is permitted, even if the sum of enlarged nodes is > 2.0 cm.

3.3.2 Uncontrolled prior invasive malignancy, excluding the current diagnosis;

3.3.3 Systemic chemotherapy for the study cancer < 2 weeks prior to registration;

3.3.4 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic;

3.3.5 HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter prior to registration. Note also that HIV testing is not required for eligibility for this protocol. This exclusion criterion is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.3.6 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields (to include Y90).

3.3.7 Prior liver transplant.

Prior to STEP TWO Randomization

3.3.8 Unable to obtain confirmation of payment coverage (insurance or other) for either possible treatment.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

(19-DEC-2025)

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

PRE-TREATMENT ASSESSMENTS

	Timeframe (calendar days)	
Assessments	**Prior to STEP 1 registration**	**Prior to treatment**
Zubrod Performance Status	30 days	
Assessment by medical oncologist who specializes in treatment of HCC	X (recommended, not required)	
CT Chest/Abdomen/Pelvis with Multiphasic Liver CT or CT Chest without contrast and MRI of Abdomen	X	
CBC w/ diff, ANC, platelets	X	
Serum creatinine, ALT, AST, total bilirubin, albumin	X	
Alkaline phosphatase, phosphate, sodium, potassium, chloride, magnesium, calcium		X
Alpha-Fetoprotein		30 days
Urine or serum pregnancy test	7 days * required only for women of child bearing potential	
PROMIS fatigue, FACT-Hep, and EQ-5D		X
Tissue banking (for consenting patients)	X	
Blood collection (for consenting patients)	X	
Informed consent	X	

ASSESSMENTS DURING TREATMENT

Assessments	During Treatment
Performance Status	Weekly
CBC w/diff, ANC, platelets	Weekly
Alkaline phosphatase, phosphate, sodium, potassium, chloride, magnesium, calcium, serum creatinine	Weekly
ALT, AST, Bilirubin	Weekly
Toxicity Assessment	Weekly

ASSESSMENTS IN FOLLOW UP

Assessments	**From end of RT: q3 mos. x 2 yrs.; q6 mos. x 3 years; then annually, unless otherwise indicated**
History/physical	X
Performance status	X
CBC w/diff, ANC, platelets	X
ALP, phosphate, sodium, potassium, chloride, magnesium, calcium	X
AFP	X
Toxicity Assessment	X
CT Chest/Abdomen/Pelvis OR CT chest without contrast and MRI of the abdomen and pelvis if contrast in contraindicated (see section 5.2.3)	X
Multi-phase liver CT or MRI (see section 5.2.3)	X
Blood collection (for consenting patients)	X (One month post RT completion, and once at the time of first progression)
FACT-HEP and EQ5D	1, 3, 6 and 12 months post RT completion
PROMIS fatigue	1 and 6 months post RT completion

Definition of Disease Assessments

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement)

of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy (30-July-2018)

Not applicable to this protocol. No anti-cancer therapies can be given concurrently with radiation including chemotherapy, targeted therapy, or immunotherapy.

5.2 Radiation Therapy (10-AUG-2022)

Treatment must start no later than 21 days after randomization.

Special Notes

- **CT based treatment planning is mandatory for this study**
- **Pre Treatment reviews for first photon and/or proton case treated at each site is mandatory. Three (3) business days are required to complete a pre-treatment review. Please see section 12.1.**
- **Image Guided Radiotherapy (IGRT) is mandatory for this study; 3DCRT, IMRT, SBRT, Cobalt based IMRT/IGRT under MRI guidance, and Protons are allowed (see Section 5.2.11).**
- **Institutional motion management strategy shall be required for all patients enrolled on this study, such as abdominal compression, gating, tracking, and breathhold (ABC) devices.**
- **Proton absorbed dose shall be reported in RBE-weighted equivalent dose (RBE correction = 1.1)**

5.2.1 Treatment Technology

All patients enrolled in this study shall be treated using an SBRT strategy. Treatment shall be delivered in 5 or 15 fractions (determined by treatment physician) over a period of 15 to 24 days, respectively. Daily pre-treatment IGRT is mandatory. Daily IGRT using MRI is permitted.

The following treatment modality/techniques are allowed for this study:

1. Photons
    a. IMRT (~1.25-10 MV)
    b. VMAT (~1.25-10 MV)
    c. 3D (~6-18 MV)
2. Protons
    a. Double Scattering (energy determined by maximum range to distal target)
    b. Pencil Beam Scanning (variable energy range, maximum value dictated by maximum range to distal target)

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical immobilization devices (e.g. vacuum immobilization,

patient positioning boards, knee cushions, and/or breath hold immobilization).

Simulation Imaging

CT scans will be required for target and normal structure definition. Multi-phasic IV contrast is recommended for the planning exam (arterial and/or venal phase imaging is recommended for GTV identification). However, due to the sensitivity of proton therapy to range variation, a non-contrast planning scan is required prior to contrast enhanced scans. Contrast enhanced scans used for proton treatment planning (dose calculation) should be avoided, alternatively fusing subsequently acquired contrast scans to aid in target delineation.

Patient immobilization strategies including custom body vacuum immobilization bags, abdominal compression, and custom fixation restraints are required. Use of implanted fiducial markers prior to planning CT is STRONGLY recommended as current radiographic imaging techniques at the treatment event (kV, MV radiograph, CBCT) do not adequately appreciate HCC target volumes. PTV margins selected should reflect institutional localization uncertainty arising from the applied patient fixation and IGRT approach.

Motion Management Technique

Motion management is required for all patients enrolled in this study. Motion management assessment should include motion sensitive imaging techniques such as 4DCT, deep inspiration/expiration CT or fluoroscopy, for this study 4DCT is preferred. Motion mitigation strategies are recommended for observed target motion > 5mm. ITV (ICRU-62), motion inclusive PTV (ICRU-83), and respiration based target localization techniques such as radiation gating using respiratory surrogates (e.g. active breathing control, visualization of external surface, active position diaphragm monitoring) are acceptable for this study.

5.2.3 Imaging for Structure Delineation, Image Registration/Fusion, and Follow-up

CT Imaging

CT exams consisting of the following shall be required for this study. The imaging exam shall include a multiphase study utilizing iodine intravenous (IV) contrast. The multiphase study shall include:

1) Non-contrast CT (planning CT)
2) Contrast-enhanced arterial phase CT – visualization of hypervascularity
3) Contrast-enhanced portal venous phase CT – visualization of vascular thrombi
4) Delayed phase CT – washout of HCC

All four scans are required for a baseline diagnosis, the arterial phase, portal phase and delayed phase scans shall be required patient follow-up.

Planning CT shall include the entire abdomen (including 4DCT as needed), contrast enhanced scans must include the entire liver at a minimum for use for target delineation.

All CT scans shall use either 2.5 or 3 mm slice thickness with an in plane resolution < = 1.5 mm.

All above multiphase imaging should be obtained in breath hold (inhale or exhale), in treatment position, when possible.

Additionally, for motion management purposes, a 4DCT should be acquired for this study. It is recommended that the reconstructed CT images – Minimum-IP, Average-IP, and Maximum-IP – shall also be created as a consequence of any 4D imaging. Should a proton treatment technique be selected, and the institutions motion mitigation strategy require the use of a selected phase or reconstructed CT from the 4DCT for dose calculation, the order of the acquired CT scans should be selected so that the CT used for dose calculation is free from contrast enhancement.

MR Imaging

MR imaging for target delineation is recommended if CT cannot be acquired due to contraindication (e.g. iodine contrast allergy). A contrast enhanced MR using gadolinium or Primovist/Eovist (Gd-EOB-DTPA) may be used unless contraindicated. A non-contrast T1 weighted image may be used if no contrast is tolerated.

Please see Section 4 for Assessments in Follow up.

5.2.4 Definition of Target Volumes and Margins

The GTV#(1,2,3) must match the lesion # on the Eligibility Checklist.

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.
Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Validation **Required/Required when applicable/Optional**
GTVp(1,2,3) _XXXX	Primary Parenchymal GTV lesions) e.g. GTVp1	**Required when applicable**

GTVv(1,2,3) _XXXX	Vascular GTV	**Required when applicable**
GTVpv(1,2,3) _XXXX	Combined parenchymal and vascular treated to same dose	**Required when applicable**
CTVp(1,2,3) _XXXX	Primary parenchymal CTV	**Required when applicable**
CTVv(1,2,3) _XXXX	Vascular CTV	**Required when applicable**
CTVpv(1,2,3) _XXXX	Combined parenchymal and vascular CTV treated to same dose	**Required when applicable**
CTVt(1,2,3) _XXXX	Prior TACE CTV treated to same dose	**Optional**
CTVr(1,2,3) _XXXX	Prior RFA CTV sites treated to same dose 1,2,…,n	**Optional**
PTVp(1,2,3) _XXXX	Primary parenchymal PTV N=1 (dominant) N>1 (subsequent)	**Required when applicable**
PTVv(1,2,3) _XXXX	Vascular PTV N=1,2,…,n	**Required when applicable**
PTVpv(1,2,3) _XXXX	Combined parenchymal and vascular PTV treated to same dose	**Required when applicable**
PTVt(1,2,3) _XXXX	Prior TACE PTV treated to same dose	**Optional**
PTVr(1,2,3) _XXXX	Prior RFA CTV sites treated to same dose	**Optional**

In the event of combining GTVs into 1or more PTVs use the table below to identify the combination and PTV. Note the GTV# must match the lesion # on the Eligibility Checklist.

Lesion	PTV Standard Naming
1	**PTV1_xxxx**
2	**PTV2_xxxx**
3	**PTV3_xxxx**
1 and 2	**PTV1_xxxx**
1 and 3	**PTV1_xxxx**
2 and 3	**PTV2_xxxx**
1, 2 and 3	**PTV1_xxxx**

Detailed Specifications
Target volumes: The definitions of volumes will be in accordance with the 1999 ICRUReport#62, except as noted below.

GTV
Describes all parenchymal and vascular HCC visualized on composite of contrast enhanced CT and MR. Primary parenchymal GTV shall be designated as GTVpN, where N is an integer indicating dominant (N=1) or non-dominant, subsequent lesions (N>1). Vascular lesions shall be designated at GTVvN, where n is an integer differentiating lesions to be treated independently (N=1,2,…,n). Parenchymal and vascular GTV may be combined if treated to the same dose, designated as GTVpvN, N being an integer differentiating lesions.

Non-tumor thrombi should not be considered as GTV, but should be included as CTV.

Non-tumor extrahepatic vascular thrombi should not be included as GTV or CTV.

CTV
Describes clinical volumes including GTV and regions at risk for microscopic disease. A CTV shall be defined for each GTV in accordance with the GTV designation nomenclature (e.g. CTVp1 corresponding to GTVp1). Additionally, the dose prescribed (in cGy) to the PTV incorporating the CTV shall be appended to the CTV name. For example, the PTVp2 treated to 60 Gy shall be named PTVp2_6000 and the incorporated CTV shall be named CTVp2_6000. For most cases, it is expected that there will be no expansion from GTV to CTV (CTV=GTV), however the following exceptions are noted to be included, with appropriate designation (if independently defined) as CTV:

1) Non-tumor vascular thrombi (designated CTVv)
2) Prior TACE sites (designated CTVt)
3) Adjacent RFA sites (designated CTVr)

PTV
Describes the volume to be used as a target for radiotherapy, a PTV shall include a designated CTV and provide an expansion margin to incorporate setup uncertainty, internal motion and delivery modality specific uncertainties (e.g. aperture margin, compensator smearing, range uncertainty and modulation width). PTV nomenclature shall follow that

defined for GTV and PTV, where individual PTV structures shall be created for all defined CTV margins (e.g. PTVv3 shall correspond to CTVv3 and GTVv3, as defined). A minimum of 4 mm symmetric margin shall be used as the lower limit for all PTV expansions. This value may be increased asymmetrically based on case specific requirements, with an upper limit of 20 mm symmetric PTV expansion. Internal motion margins are explicitly included in the PTV calculation, where actual values are obtained from patient specific motion imaging (such as 4DCT).

Additionally, for proton therapy techniques, an additional margin must be included to compensate for range uncertainty at the distal surface of the defined PTV. Per ICRU Report 78, a range uncertainty margin shall be added, where the distal target range is calculated according to the following recipe: proton distal range = maximum range to distal surface of CTV + range uncertainty (= 0.035*maximum distal range) + setup-margin + Internal motion margin.

5.2.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.
Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Validation **Required/Required when applicable/Optional**
Liver	Liver	**Required**
Liver-GTV	Normal, non-GTV liver	**Required**
Esophagus	Esophagus	**Required when applicable**

Stomach	Stomach	**Required**
Duodenum	Duodenum	**Required**
Bowel_Small	Small Bowel	**Required when applicable**
Bowel_Large	Large Bowel	**Required when applicable**
SpinalCord	Spinal Cord	**Required**
SpinalCord_PRV	Spinal Cord + 5mm margin expansion	**Required**
Kidney_R	Right Kidney	**Required when applicable**
Kidney_L	Left Kidney	**Required when applicable**
Kidneys	Left Kidney + Right Kidney	**Required when applicable**

External	Patient body contour	**Required**
ChestWall	Chest Wall	**Required when applicable**
GallBladder	Gall Bladder	**Required when applicable**
BileDuct_Common	Common Bile Duct	**Required when applicable**
Heart	Heart	**Required**
V_VenaCava_I	Inferior Vena Cava	**Required when applicable**

Detailed Specifications

- **Liver: Boundaries: Whole Liver**
- **Liver-GTV: Boundaries: Boolean subtraction, Liver – GTV(all)**
- **SpinalCord:** Boundaries: Level of PTV, 10 cm above/below level of PTV or any region involving dose > 5 Gy.
- **SpinalCord_PRV:** Boundaries: Uniform 5 mm expansion in all directions with respect to Spinal Cord.
- **Esophagus:** Boundaries: Level of PTV, 10 cm above level of PTV or any region involving dose > 5 Gy;
- **Stomach:** Boundaries: whole stomach
- **Duodenum:** Boundaries: whole duodenum
- **Bowel_Small:** Boundaries: all to 10 cm below lowest level of liver and covering dose > 5 Gy
- **Bowel_Large:** Boundaries: all to 10 cm below lowest level of liver and covering dose > 5 Gy

- **Kidney_R:** Boundaries: Whole kidney
- **Kidney_L:** Boundaries: Whole kidney
- **Kidneys:** Boundaries: Boolean addition, Right Kidney + Left Kidney
- **External:** Boundaries: 10 cm above/below all field projections, entrance, and exit, to termination of CT
- **ChestWall:** Boundaries: Level of PTV and covering dose > 10 Gy
- **GallBladder:** Boundaries: Whole volume
- **Common Bile Duct** (**BileDuct_Common**): Boundaries: Whole volume
- **Heart: Boundaries:** Level of PTV and including regions covering dose > 5 Gy
- **Inferior Vena Cava** (**V_VenaCava_I**)**:** Boundaries: Level of PTV and including regions covering dose > 10 Gy

5.2.6 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Cases will be scored using the Compliance Criteria table.

All dose values reflect absorbed physical dose for photons and RBE-weighted dose for protons (where RBE correction = 1.1)

For 5 fraction SBRT fractionation schemes (proton, photon)

Target Standard Name	# of fractions	Dose specification technique
PTVp(1,2,3)_XXXX, PTVv(1,2,3)_XXXX, PTVpv(1,2,3)_XXXX PTVt(1,2,3)_XXXX PTVr(1,2,3)_XXXX	5	Covering 95% of PTV

Where XXXX is the target dose in cGy (e.g. PTVp_5000)

Note: Dose to PTV is dependent on normal liver dose according to the following protocol. Liver dose shall be assessed using Mean Liver-GTV dose. PTV dose for purposes of this table includes all volumes contained within (completely or in part) the whole Liver volume.

Allowed PTV Dose	Liver-GTV Mean Dose
50 Gy	≤ 13 Gy
45 Gy	≤ 14 Gy
40 Gy	≤ 15 Gy
35 Gy	≤ 15.5 Gy
30 Gy	≤ 16 Gy

For 15 fraction conventional fractionation schemes (photon, proton)

Target Standard Name	# of fractions	Dose specification technique
PTVp(1,2,3)_XXXX, PTVv(1,2,3)_XXXX, PTVpv(1,2,3)_XXXX PTVt(1,2,3)_XXXX PTVr(1,2,3)_XXXX	15	Covering 95% of PTV,

Note: Dose to PTV is dependent on normal liver dose according to the following protocol. Liver dose shall be assessed using Mean Liver-GTV dose. PTV dose for purposes of this table includes all volumes contained within (completely or in part) the whole Liver volume.

Allowed PTV Dose	Liver-GTV Mean Dose
67.5 Gy	≤ 20.5 Gy
58.05 Gy	≤ 21.2 Gy
52.5 Gy	≤ 21.9 Gy
45 Gy	≤ 22.5 Gy
37.5 Gy	≤ 28 Gy

5.2.7 Compliance Criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable.

Normalization of Dose: The plan is normalized such that 95% of the PTVp, PTVv, and/or PTVpv volume receives prescription dose specified by protocol (defined in Section 5.2.6). All PTVs must be treated to these criteria. PTV margins may not be adjusted to accommodate these criteria. Target volume constraints are acceptable for 5 and 15 fraction treatment schemes, proton, or photon.

All dose values are correct for photon absorbed dose and proton RBE-weighted dose (proton RBE correction = 1.1).

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Target Volume Constraints and Compliance Criteria (all fractionation schemes)

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTVp(1,2,3)_XXXX, PTVv(1,2,3)_XXXX, PTVpv(1,2,3)_XXXX PTVt(1,2,3)_XXXX PTVr(1,2,3)_XXXX	D95%[Gy]	≥95% Rx Dose	≥90% Rx Dose
	D99%[Gy]	≥95% Rx Dose	≥85% Rx Dose
	D0.03cc[Gy]	≤120% Rx Dose	≤150% Rx Dose

Per Protocol range is excluded from Variation Acceptable range.

Normal Structure Constraints and Compliance Criteria
Constraints for 5 fx SBRT treatment technique (protons, photons RBE-corrected)

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Endpoint/Notes
Liver-GTV	ΔMean[%]	1%	2%	Defined per dose escalation protocol in section 5.2.6
Esophagus	D0.5cc[Gy]	< 30	< 34	
Stomach	D0.5cc[Gy]	< 30	< 32	
Duodenum	D0.5cc[Gy]	< 30	< 32	
Bowel_Small	D0.5cc[Gy]	< 30	< 32	
Bowel_Large	D0.5cc[Gy]	< 32	< 34	
SpinalCord_PRV	D0.5cc[Gy]	< 25	<28	
Kidneys	D33%[Gy]	< 15	< 17	
	Mean[Gy]	< 10	< 12	
	D10%[Gy]	< 7	< 8	Criteria used if only single kidney functional
Heart	D0.5cc[Gy]	< 20	< 22	
ChestWall	D2.0cc[Gy]	< 35	< 40	

Per Protocol range is excluded from Variation Acceptable range.

Constraints for 15 fraction conventional treatment scheme

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Endpoint/Notes
Liver-GTV	ΔMean[%]	1%	2%	Defined per dose escalation protocol in section 5.2.6
Esophagus	D0.5cc[Gy]	< 40	< 45	
Stomach	D0.5cc[Gy]	< 40	< 45	
Duodenum	D0.5cc[Gy]	< 40	< 45	
Bowel_Small	D0.5cc[Gy]	< 40	< 45	
Bowel_Large	D0.5cc[Gy]	< 40	< 45	
SpinalCord_PRV	D0.5cc[Gy]	< 30	< 35	
Kidneys	V18Gy[%]	< 30	< 32	
	V10Gy[%]	< 60	< 64	Criteria used if only single kidney functional
Heart	D0.5cc[Gy]	< 30	< 34	
ChestWall	D2.0cc[Gy]	< 40	< 45	

Delivery Compliance criteria

	Per Protocol	Variation Acceptable	Notes
Start date	< 21 days	None	
Overall Treatment days	15 days	21 days	5 fraction, SBRT treatment scheme
Overall Treatment days	24 days	29 days	15 fraction, conventional treatment scheme
Interruptions	14 days	None	

5.2.8 Treatment Planning Priorities and Instructions

Critical Structure and Target priorities must be listed in order of decreasing importance.

1. SpinalCord_PRV2. Stomach, Duodenum
3. Bowel_Small, Bowel_Large
4. Kidneys
5. PTV(all)
6. Heart
7. ChestWall
8. GallBladder
9. BileDuct_Common

- Required algorithms
  - Photon: Superposition/Convolution, Monte Carlo
  - Proton: Pencil Beam, Monte Carlo

Acceptable choices of algorithm are listed at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. Any algorithm used for this study must be credentialed by Imaging and Radiation Oncology Core (IROC) Houston.

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported. These principles hold for Pencil Beam type algorithms and for homogeneous dose calculations when allowed for a clinical trial (e.g., conical collimators in stereotactic radiosurgery).

5.2.9 Dose Calculations

- Primary dataset for dose calculation

The primary dataset for dose calculation must be a free-breathing CT that was acquired along with 4DCT, an average intensity pixel CT (AveIP) generated from the 4DCT, the breath-hold/gated CT, or the free-breathing CT acquired with no other motion management. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density. As mentioned previously, in the case of proton radiotherapy, the treatment

planning CT must be devoid of contrast, no contrast overrides, due to range uncertainty issues are allowed.

-Dose matrix resolution
Dose grid size should be ≤ 2 mm in all directions.

5.2.10 Patient-Specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

For IMRT/VMAT/proton plans, patient specific QA is highly recommended. Any patient-specific QA performed should follow your institutional guidelines. The recommended patient specific QA criterion is for 90% of the comparison points to pass a ±3%/3mm Gamma Index analysis. If SBRT is used, 90% pass is recommended using a ±3%/2mm Gamma Index analysis.

For passive scattered or uniform scanned beam plans that utilize a patch field, patient specific QA must be performed with the compensator.
For IMPT plan QA, measurement in multiple layers is required.

5.2.11 Daily Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

<u>Guidelines for IGRT</u>

- For all treatment schemes daily setup imaging shall be required
- 3D daily setup imaging is strongly recommended for all treatments
- 3D daily setup imaging is required for targets not delineated with implanted fiducials
- Image registration techniques:
    - Orthogonal kV (2D)
        - Fiducial markers, bony anatomy, diaphragm
        - Breath hold imaging recommended
    - Volumetric 3D (kV/MV)
        - Fiducial markers, bony anatomy, diaphragm
        - Average-IP as reference for free-breathing CBCT
        - Selected a phase 4DCT as reference for a particular breath hold CT/gated CBCT
        - Free-breathing CT is not to be used as reference for treatment localization
- Frequency for localization checks
    - SBRT 5 fraction schemes
        - Treating physician shall provide localization check prior to each treatment
        - Physicist shall provide localization check prior to first treatment

    - SBRT 15 fraction schemes
        - Treating physician shall provide weekly localization check
        - Physicist shall provide localization check prior to/at start of first treatment
- Target corrections should be made if observed registration result not within prescribed PTV margins
    - A maximum PTV expansion of 20 mm and 4mm in minimum is allowed for this study
    - Positional correction is required when daily setup variation exceeds 4mm
    - Patients that exceed setup tolerances corresponding to maximum PTV expansion limit for more than a defined fraction limit must be excluded from the study
        - 5 fraction SBRT scheme: 1 fraction limit
        - 15 fraction SBRT scheme: 3 fraction limit
- All treatment position corrections from each treatment shall be recorded and reported

When orthogonal kV imaging is employed for sites where respiratory motion is not controlled via motion management techniques, care must be taken to ensure accurate targeting of the PTV within the treatment

5.2.12 Management of Radiation Dose to the Patient from IGRT

NRG Oncology is concerned about the estimated doses given from IGRT, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

5.2.13 Radiation Therapy Adverse Event Reporting

See Section 7.3 for details on adverse event reporting.

5.2.14 Radiation Therapy Toxicity Assessment During Therapy

The criteria used for grading toxicities on case report forms (CRFs) that occur on this study from activation through May 9, 2018 are the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The criteria used for grading toxicities was upgraded to version 5.0 on May 10,2018 and will be used for all toxicity reporting from that date going forward.

Common (20-100%)

- Fatigue (which generally goes away after the radiation therapy is completed)
- Skin irritation, redness, itchiness, discomfort in the treatment area
- Lymphopenia

Occasional (4-20%)

- Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal tract irradiated

- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction, or changes in motility following therapy (may require medications or surgery) (<10% permanent changes)
- Chest wall pain, rib fracture (< 10%)
- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease.

Rare, but serious (<3%)

- Radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly, and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

Patients will be assessed weekly during radiation therapy for toxicity (as per Section 4.0). Unless the treating physician recommends continuation, radiation therapy should be held per the treatment modification criteria (as per Section 6.0) with possible continuation of radiation if toxicity resolves.

5.2.15 Radiation Modification – See Section 6

5.2.16 Case Review

NOTE: PRE-TREATMENT REVIEWS are required for the first case enrolled from each site. These first cases at each institution will require approval prior to administering any protocol RT.

The Principal Investigators will perform ongoing remote RT Quality Assurance Review after cases enrolled have been received at IROC Philadelphia-RT QA Center. The Pre-Treatment review process requires three (3) business days to complete a pre-treatment review, once all complete and correct data is received at IROC Philadelphia-RT. If an unacceptable deviation occurs, the next case may require a Pre Treatment Review. After institutions have passed the pre-treatment review of the first proton and first photon cases enrolled, review of all other cases will be ongoing and performed remotely for all patients.

5.3 General Concomitant Medication and Supportive Care Guidelines (18-OCT-2019)

Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Herbal and Nutritional Supplement

The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, basic multivitamins , L-glutamine, or probiotics oral supplements will be permitted either at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins are not allowed.

- *Anticonvulsants*
- *Antiemetics*
- *Anticoagulants*
- *Antidiarrheals*
- *Analgesics*
- *Hematopoietic Growth Factors*
- *Highly active antiretroviral therapy (HAART)*

5.3.1 Participation in Other Trials

During treatment and prior to progression, patients will not be allowed to participate simultaneously in other therapeutic trials for cancer (imaging, biomarker and Quality of Life studies are permitted).

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 7,
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

6. TREATMENT MODIFICATIONS/MANAGEMENT (30-JULY-2018)

Radiation Modification Table/Recommended Treatment Delay Criteria

TOXICITY	MODIFICATION
<u>Hematologic Toxicities</u>	
grade 1 or 2	Continue radiation
grade 3 (excluding lymphopenia)	Hold radiation until ≤ grade 2, then continue
grade 4 (excluding lymphopenia)	Hold radiation 1 week and until ≤ grade 2, then continue
<u>Gastrointestinal Toxicities</u>	
grade 1 or 2 diarrhea	Continue radiation

grade ≥ 3 diarrhea	Hold radiation until improves to ≤ grade 2, then resume
grade 1 or 2 nausea or vomiting	Initiate anti-emetics prior to radiation and as needed and continue radiation
grade 3 nausea or vomiting	Hold radiation until improves to ≤ grade 2, then resume with anti-emetics prior to radiation and as needed
Hepatic Dysfunction	
bilirubin 1.3-4.7 mg/dL	Continue radiation
bilirubin > 4.7 mg/dL	Hold radiation until improves to ≤ 4.7, then resume
grade 1 or 2 AST or ALT	Continue radiation
< 10x ULN AST or ALT	Continue radiation
> 10x ULN AST or ALT	Hold radiation until improves to ≤10x ULN AST or ALT, then resume
grade 4 AST and ALT	Hold radiation for one week and until improves to ≤10x ULN AST or ALT, then resume
grade 1, 2, or 3 Alk phos	Continue radiation
grade 4 Alk phos	Hold radiation for one week and until improves to ≤ grade 3, then resume
Other non-hematologic Toxicities	
grade 1, 2	Continue radiation
grade 3	Hold radiation until improves to ≤ grade 2, then resume
grade 4	Discontinue radiation

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Not applicable to this protocol

7.2 Adverse Events and Serious Adverse Events (30-July-2018)

7.2.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and CRFs. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study CRFs forms will continue to use CTCAE version 4.0 through May 9, 2018. Beginning May 10, 2018, adverse event reporting in CRFs will be collected in CTCAE version 5.0.

All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/ protocolDevelopment/electronic_applications/ctc.htm

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Expedited Reporting of Serious Adverse Events (19-DEC-2025)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology by phone, (1-215-574-3191). An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.3.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. For instructions to submit supporting documentation, contact NRG Oncology (1-215-517-3191)).
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as “an action *not* recommended” must still be reported to fulfill NRG safety reporting obligations. Sites

must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.3.2 Expedited Reporting Requirements for Serious Adverse Events

Any Phase Study Utilizing Radiation Therapy [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE 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).

SAEs (as defined by the above criteria) that meet the reporting requirement in the table below **MUST** be immediately reported via CTEP-AERS within the timeframes detailed in the table below.

Unexpected and Related Grade 4 SAE Reporting Timeframes	All Grade 5 SAE Reporting Timeframes
15 Calendar Days	15 Calendar Days

[1]SAEs that occur more than 30 days after the last administration of protocol treatment and have an attribution of possible, probable, or definite require reporting as follows:

15 calendar day report for:

- Unexpected Grade 4 s and Grade 5 SAEs

7.4 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5 Secondary Malignancy (18-OCT-2019)

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.

CTEP requires all secondary malignancies following radiation therapy must be reported via CTEP-AERS. 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.

Second Malignancy:
A second malignancy is one **unrelated to the treatment of a prior malignancy** (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine AE reporting unless otherwise specified.

7.6 Routine Reporting Requirements for Adverse Events (18-OCT-2019)

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

8. REGISTRATION, STUDY ENTRY PROCEDURES (19-DEC-2025)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.RCR utilizes four person registration types that are applicable to this study.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges; and
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting **person** in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures (19-DEC-2025)

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the

CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Holds an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-GI003 Site Registration

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol specific requirements (PSRs).
- IRB/REB Approved Informed Consent (International sites only: English and native language versions*)

  ***Note**: International and Canadian Institutions must provide certification/verification of IRB/REB IEC consent translation to NRG Oncology (described below).

  *Translation of regulatory documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations, access the Provider

Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Site must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. Only an individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory and Roster Maintenance applications to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

8.1.1 Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select NRG Oncology and protocol number NRG-GI003.
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type*filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.2 Letter of Intent –ALL SITES

NOTE: **All sites** must submit a Letter of Intent (LOI) to NRG Oncology Regulatory to receive approval to participate in this trial. For more details see CTSU protocol specific page.

8.3 RT-Specific Pre-Registration Requirements (10-AUG-2022)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification.

Proton centers wishing to participate in this study must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the IROC Houston (http://irochouston.mdanderson.org) and IROC (https://www.irocqa.org) websites. These requirements include, but are not limited to, completion of a proton facility questionnaire, a successful IROC-Houston site visit, which identifies the proton technique(s) which can

be used, annual monitoring of the proton beam calibration, e.g. IROC Houston's monitoring program, and successful digital data submission to TRIAD. Once these requirements are successfully met, the proton center is approved to use proton therapy in NCI sponsored clinical trials. Each trial may require additional proton therapy credentialing steps prior to being allowed to enter a patient treated with protons onto a specific study. IROC Houston will coordinate the completion of the proton therapy use approval process in conjunction with the appropriate other IROC QA Centers for any additional protocol specific credentialing requirements. See the table below for the credentialing requirements of this study.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**		
	Treatment Modality		
	Photon	Proton	Key Information
Facility Questionnaire	**x**	**x**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Credentialing Status Inquiry Form	**x**	**x**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Phantom Irradiation	**x**	**x**	A liver phantom irradiation (photon or proton, depending on the delivery modality used) provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**). Note that only the most sophisticated technique needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used.
IGRT Verification Study	**x**	**x**	Instructions for IGRT credentialing may be found on the IROC Houston website (**http://irochouston.mdanderson.org**).
Credentialing Notification Issued to:			
Institution	Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met. The site will need to upload a PDF of the approval email to the CTSU Regulatory Portal for RSS to be updated.		

8.4 Digital Radiation Therapy Data Submission Using Transfer of Images, and Data (19-DEC-2025)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.5 Patient Enrollment (19-DEC-2025)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.5.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of

Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (RCR).

Prior to accessing OPEN site staff should verify the following:
- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

NOTE: Step 2 of registration requires a second web registration for all patients. If a patient is not going on to randomization, step 2 of registration must still be completed via OPEN.

9.0 DRUG INFORMATION

Not applicable to this protocol.

10.0 PATHOLOGY/BIOSPECIMEN

10.1 Biospecimen Submission Tables

10.1.1 Optional Specimen Submissions

(Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.)

10.2 Tissue Selection for Integrated marker testing:

10.2.1 Marker to be tested and its usage

Identifying a prognostic/predictive biomarker for increased risk of disease progression or toxicity (liver dysfunction) would be highly desirable. We found that high plasma HGF levels also associated with shorter OS in HCC and ICC patients treated with protons alone (Hong 2016). Previously, investigators from University of Michigan reported that high levels of serum HGF one month after radiation predicted for increased risk of hepatic dysfunction (Lawrence et al). Given this published exploratory work, circulating HGF will be definitively evaluated as a biomarker of response and/or toxicity in this trial. The measurements will be done in a CLIA-certified core under the supervision of Dr. Dan Duda.

10.2.2 Testing requirements and reporting:

- Testing will be performed in a CLIA-certified and licensed testing facility, with results reported per Standard Operating Procedure (SOP).
- Results will then be communicated to NRG Oncology.

10.2.3 Method of testing:

Sample collection and storage for plasma samples

- 10 mls peripheral blood is collected in EDTA (purple top) tubes at each study site and placed on wet ice
- Samples are transported on wet ice to/by the technician at each site
- The technician will immediately process the samples
- Plasma is separated in 2 ml aliquots, and stored in cryovials at –80º C
- See detailed specimen collection/processing/shipping instructions on the protocol specific page of the CTSU website: https://www.ctsu.org/Public/Default.aspx?ReturnUrl=%2f

Acceptable Plasma Samples

1) EDTA plasma samples collected and stored as described above
2) Frozen plasma samples can be thawed 2 times.

Unacceptable Plasma Samples

1) Plasma collected in tubes other than EDTA tubes
2) Hemolysed plasma (pink to bright red)
3) Lipemic plasma (turbid, cloudy, or milky)
4) Icterus plasma (dark to bright yellow)

Protocol of the Procedure – ELISA and multiplexed array

The procedure is done in the following sequence:

1) Thaw plasma samples on ice
2) Centrifuge samples at 10,000 rcf for 10 min at 4º C
3) Bring all reagents to room temperature (18-25º C)
4) Shake plates on shaker at 750 rpm (300-1000 rpm)
5) Prior running the plate on the SI-2400 instrument, check the "Status" of the camera temperature (should be –24.95ºC)
6) After the procedure either re-freeze or throw away the samples (if they have already been thawed twice) into the biohazard container.

The results of the tests will be numerical values (concentration of the analyte in

plasma). For analysis of the integrated biomarker (plasma HGF concentration), we will use an initial cut-off of 1,500 pg/ml (Hong 2014). Samples below the lowest level of quantification (LLOQ) will be given a value equal to LLOQ for the purpose of analysis.

Table: Biomarker assay validation parameters

Validation parameter	Acceptance Criteria
Standard Curve Precision and Accuracy	A minimum of 75% of the standards must have a mean accuracy within 80-120% of the nominal value, except at the LLOQ and ULOQ where the accuracy can be within 75-125% of nominal. The precision (CV) for each standard must be equal to or less than 20%, except at the LLOQ and ULOQ where the CV can be equal to or less than 25%.
Assay Range	The assay range is defined by the LLOQ and ULOQ.
Intra-Assay Precision	The intra assay CV of five sets of the validation samples (VS) measured on one day must be equal to or less than 20%, except at the LLOQ and ULOQ where the CV can be equal to or less than 25%.
Intra-Assay Accuracy	The intra assay accuracy should be between 80-120% of the nominal value, except at the LLOQ and ULOQ where the mean accuracy can be within 75-125% of nominal.
Inter-Assay Precision	The CV of six sets of the VS measured on 6 different days must be equal to or less than 20%, except at the LLOQ and ULOQ where the CV can be equal to or less than 25%.
Inter-Assay Accuracy	The inter-assay accuracy should be between 80-120% of the nominal value, except at the LLOQ and ULOQ where the mean accuracy can be within 75-125% of nominal.
LLOQ and ULOQ	The LLOQ and ULOQ are defined by the lowest and highest validation samples, respectively, that meet the acceptance criteria for inter- and intra-assay precision and accuracy.
Dilution Linearity	The mean concentrations for each dilution that falls within the assay range must be equal to or within 75-125% of the nominal value (after multiplying by the dilution factor) and have CVs equal to or less than 25% (after multiplying by the dilution factor).
Prozone Effect	Samples with a concentration above the ULOQ should be measured > ULOQ in order to exclude a prozone effect.
Selectivity	Plasma samples from 6-10 individuals to be measured with and without HGF. A minimum of 80% of the spiked matrices must be equal to or within ± 25% of the nominal value.
Stability	The mean concentration of HGF measured in stability samples must be within 75-125% of the nominal value and should have a CV equal to or less than 25%. <u>Conditions:</u> Short term (bench-top) stability: RT, 0/5 h Short term (2-8ºC): 2-8ºC, 0/1/3 days Long term stability: -80ºC, 0/1/2/3/6 month Freeze/thaw stability: 0/1/2/3 cycles
Parallelism	4-6 individual plasma samples with high endogenous HGF concentration to be measured in 2-fold serial dilutions without additional spiking. The mean of the dilution corrected concentrations for all the dilutions that fall within the assay range must have a CV less than or equal to 25%.

Specificity	The mean concentration of the analytes measured in samples spiked with the individual analytes must be within 75-125% of the nominal concentration for the given analyte.

10.3 Location of testing

All biomarker analyses will be done in a CLIA-certified Core Laboratory under the supervision of Dr. Dan G. Duda. All plasma samples will be stored at –80ºC at the NRG Oncology Biobank and shipped on dry ice to Dr. Duda upon completion of the study.

10.4 Tissue Submission for testing: See Biospecimen Submission tables below. (18-OCT-2019)

Specimen Collection for Banking for Future Research

Specimens are being collected for future translational research projects.

- Required Forms: ST form, pathology reports. All forms must be completely filled out with an NRG Label including the Study #, Case #, NRG Institution number or Institution NCI ID, and patient initials. The pathology accession number and date of procedure must remain visible on the pathology report but all other PHI information must be redacted/removed.
- Kits are available for Frozen biospecimens from the NRGBB-SF. Sites should include the following information in their email: their ship to Fed Ex address with room number, confirm site has IRB approval for study, how many patients site enrolled in past month. A maximum of 2 kits per site may be requested.
- Detailed Processing and shipping instructions can be found on the protocol specific page of the CTSU website: https://www.ctsu.org/Public/Default.aspx?ReturnUrl=%2f
- Shipping days for Frozen Specimens: Monday-Wednesday (U.S. sites); Monday-Tuesday. International sites must contact the bank before shipping. Check NRG Broadcasts for bank holiday closures. We are unable to accept shipments on Saturdays or holidays. Check Fed Ex site for storm delays and do not ship frozen biospecimens during severe weather.
- Shipping costs: A single use prepaid Fed Ex label is provided for each case in GI003 kits provided to the site for batch shipping frozen biospecimens to the NRGBB-SF. Ship all Biospecimens for banking to:

  NRG Oncology Biospecimen Bank – San Francisco
  2340 Sutter Street- Room S341
  UCSF
  San Francisco, CA 94115
  415-476-7864/Fax 415-476-5271
  Email: NRGBB@ucsf.edu

For questions about kits or banking biospecimens contact:
NRG Oncology Biospecimen Bank – San Francisco
NRGBB@ucsf.edu
415-476-7864/Fax 415-476-5271

Specimen Type	**Collection Time Points**	**Collection Information and Requirements/Instructions for Site**	**Shipping** *See protocol-specific page of the CTSU website for detailed specimen collection and shipment instructions]*
Specimen 1 H&E slide(s) of Primary tumor	Pre-treatment	H&E stained slide. Slide can be a duplicate cut slide, does not have to be the diagnostic slide. Forms: *ST, Pathology report*	Ship ambient to NRGBB-SF
Specimen 2 FFPE Block (same as H&E)	Pre-treatment	Block should match the H&E being submitted. The bank cannot evaluate blocks without corresponding H&Es. Site should make every effort to submit the block for this study. If Site is unable to submit a Block then the following alternative is acceptable: A) Two 2mm (or 3mm) punches (tumor size dependent) embedded in paraffin with a corresponding H&E (punch kits available from NRGBB-SF upon request) Note: Unstained slides are not an acceptable alternative for tissue/punch blocks for banking studies.	Ship ambient to NRGBB-SF (use cold packs during warm weather)
Specimen 3 2 Plasma- EDTA tubes 5-10 mL of anticoagulated whole blood in EDTA tubes #1&2 (purple/ lavender top) and centrifuge	Pre-treatment Post treatment – One month post RT completion, and once at time of first progression	Frozen plasma samples containing minimum 1.**0 mL per aliquot** in 2 mL cryovials (six) For protocol-specific plasma processing, refer to protocol section 10.2.3 and the processing instructions on the CTSU website. Storage: -80°C and ship frozen	Ship on Dry Ice by Priority Overnight Courier to NRGBB-SF
Specimen 4: Serum- Red top tube 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-treatment Post treatment – One month post RT completion, and once at time of first progression	Frozen serum samples containing minimum **0.5 mL per aliquot** in 1 mL cryovials (five) Storage: -80°C and ship frozen	Ship on dry ice by overnight courier to NRGBB-SF
Specimen 5: Whole Blood-EDTA tube Whole blood for DNA: 5-10 mL of	Pre-treatment *If site missed this collection, they may collect at any other time but must note this on the ST form when submitting*	Frozen whole blood containing 1.5 mL per aliquot in 2 mL cryovials (three) Storage: -80°C and ship frozen	Ship on dry ice by overnight courier to NRGBB-SF

anticoagulated whole blood in EDTA tube #3 (purple/lavender top) and mix			

11.0 SPECIAL STUDIES (NON-TISSUE)

11.1 Patient Reported Outcomes (PROs) (30-July-2018)

Patient reported outcomes (PROs) in HCC is understudied, but clearly of importance due to the expected poor overall survival in patients with advanced HCC, the co-morbidities that exist in these patients, the near universal presence of underlying liver disease and the potential for serious toxicity (notably liver) to occur from radiation treatment. Patients who never initiate NRG-GI003 study therapy or who experience disease progression should continue participating in the QOL study.

There are few published prospective studies using validated questionnaires to assess longitudinal PROs in patients with HCC receiving stereotactic body radiotherapy (SBRT). In an early trial of 28 patients (9 HCC) not suitable for other treatments, given 3- or 5-fraction SBRT to doses 25 to 37.5 Gy and completing the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) at baseline and 1, 3, and 6 months after treatment, only fatigue at 1 month showed a statistically significant change from baseline (P=.004), (Mendez Romero 2008). Law et al administered the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) to 33 patients with liver-confined HCC before, immediately after, and 3 and 6 months after treatment with 55 Gy in 10 fractions (Law 2012). Only a trend to worsening PROs at 6 months (P=.09) was noted. Klein and colleagues recently reported on prospective PRO assessment in liver metastases and HCC patients receiving SBRT (Klein 2015). In this phase I/II study of SBRT for unresectable liver cancers (35% HCC), PROs using the FACT-Hep and the EORTC QLQ-C30 was collected at baseline, and at 1, 3, 6 and 12 months post-treatment. Appetite loss and fatigue statistically worsened by 1 month after treatment but recovered by 3 months. At 3 and 12 months after treatment, respectively, the FACT-Hep score had improved relative to baseline in 13%/19%, worsened in 36%/27%, and remained stable in 51%/54%. Using the QLQ-C30 Global Health score, PROs improved in 16%/23%, worsened in 34%/39%, and remained stable in 50%/38% at 3 and 12 months, respectively. Interestingly, patients with small tumors 6 cm or less in diameter did not experience a clinically significant decline in PROs at any time point, in contrast to the overall group. This finding suggests that patients with less normal liver irradiated may experience stable or improved PROs as compared to baseline.

There have also been a few retrospective reports of PROs in patients receiving proton verses photon therapy for other primary cancer sites. In 35 patients with oropharyngeal cancer, investigators from the MDACC evaluated the MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) before treatment, during proton or photon therapy, within the first 3 months after treatment and in longer follow-up (SIO 2016). Changes in taste and appetite during the first 3 months post therapy and in long term follow-up favored proton therapy (P<0.048). Similarly, investigators from MD Anderson

used the same MDASI instrument to measure PROs in 82 patients who underwent 3DCRT, IMRT or proton therapy for non-small cell lung cancer (Wang 2016). The proton group received a significantly higher radiation target dose than did the IMRT and 3DCRT groups ($P< 0.001$). The systemic symptoms fatigue, drowsiness, disturbed sleep, and lack of appetite worsened significantly in the 3DCRT and IMRT groups but not in the proton group during and immediately after radiation, supporting the authors hypothesis that less severe symptom burden was associated with an enhanced normal tissue protection. The 3DCRT and IMRT groups did, however, report a greater decrease in systemic symptoms (fatigue, drowsiness, lack of appetite, disturbed sleep) after therapy.

Due to the paucity of PROs data in HCC and the potential benefit of proton SBRT over photon SBRT in normal tissue sparing (most notably normal liver) and local control (due to achievement of higher tumor doses), it will be important to measure differences in PROs in HCC patients treated with protons as compared to photons on this trial. If proton therapy is associated with a sustained reduction in the burden of HCC with a better toxicity profile as compared to proton therapy, it may lead to improved PROs.

Moreover, the inflammatory response resulting from exposure to ionizing radiation is an important aspect in proton applications, especially concerning the induction of normal tissue complications. Some data in terms of post-therapy inflammation are available from clinical studies, where patients treated with photons plus protons and with protons only were compared (Gridley 2004). A significantly higher expression of proteins involved in the inflammatory response was observed in patients receiving photons, with 62% of them developing serious negative pulmonary changes (scored as 2 or greater). In contrast, none of the patients treated only with protons showed such serious side effects. At the same time, limited and controversial data may be found in the literature, coming from studies conducted *in vitro* as well as with animal models (Kajioka 2000, Rithidech 2010). As increased fatigue as reported by the FACT instrument has been shown to correlate with increases serum levels of interleukin 2 (IL-3), IL-8, IL-9, IL-10, IL-16, interferon γ-induced protein 10, interferon α2, interferon γ, and stromal cell-derived factor 1α following prostate cancer radiation (Feng 2016), an important future laboratory correlate of this study may be to evaluate the serum inflammatory and cytokine response and compare to both treatment modality and PROs.

As such, the primary PRO hypothesis for this trial will be:

Proton SBRT will be associated with significantly less patient reported fatigue than photon SBRT at 1 month post completion of therapy. This will be measured by the PROMIS fatigue (see below for instrument description and administration time points). As already discussed, the PRO studies to date have shown increased fatigue from the patients' perspective at 1 month after SBRT for liver cancers (Klein 2015, Mendez Romero 2008).

As the prospective longitudinal PRO data for liver cancer is sparse, and we may observe differences between protons and photons, we will also examine overall QOL post

treatment completion, as measured by FACT-Hep version 4.

The FACT-Hep will be used (in contrast the EORTC instrument). Klein and colleagues showed similar longitudinal PROs in this patient population with both instruments, and NRG Oncology is currently using the FACT-Hep for the ongoing NRG/RTOG 1112 trial evaluating if the addition of SBRT to sorafenib for patients with HCC improves PROs at 6 months post initiation of therapy.

This analysis will be more exploratory in nature, but the totality of the SBRT and proton data suggest that PRO changes may be seen post therapy and in follow-up.

The PROMIS fatigue short form version 1.0 8a will be collected at baseline and at 1 month and 6 months post RT treatment completion. The FACT Hep version 4 will be collected at baseline, and then at 1, 3, 6 and 12 months post RT treatment completion.

PROMIS fatigue short form version 1.0 8a
Fatigue will be measured with the PROMIS short form, version 1.0 8a. This questionnaire contains 8 questions related to severity, bother and activity interference related to fatigue. Responses are “not at all” to “very much” for 6 questions; and “never” to “always” for 2 questions. The perspective is in the last 7 days. The PROMIS measures have demonstrated good reliability and validity with a subset of 7 items correlating with the full fatigue item bank (95 items) (Cella 2010, 2016).

Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep)
The FACT-Hep version 4 questionnaire will be used to measure QOL. The FACT-Hep is a 45-item self-report instrument designed to measure health-related quality of life (HRQL) in patients with hepatobiliary cancers. The FACT-Hep consists of the 27-item FACT-General (FACT-G), which assesses generic QOL concerns, and the newly validated 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues. Patients are asked to score each item for the past week on a 4-point likert scale (from 0 “not at all” and 4 “very much”). The total FACT-Hep score is the sum of the four sub-scale scores and ranges from 0 to 108; it takes less than 15 minutes to complete and is translated in 45 languages. The FACT-Hep is validated and presents good internal consistency, test–retest reliability, and convergent and discriminate validity in patients with hepatobiliary cancer and HCC (Heffernan 2002, Steel 2004, Steel 2006, Wang 2007).

11.2 Quality-Adjusted Survival

Patient-reported outcomes (PROs) are increasingly being incorporated into clinical trials for documentation of effects of treatment not measured by traditional endpoints, such as overall survival. This is important with interventions that may increase treatment-related side effects without positively impacting survival. For instance, in this trial, photon SBRT may be associated with similar survival to proton SBRT, but may be associated with significantly more toxicity.

Quality-adjusted survival is an endpoint that incorporates a patient’s utility or preference

of the health state that is combined with the time spent in that health state (Glasziou 1990). The resultant is a quality-adjusted life-year (QALY). Utility can be measured by different methods including Standard Gamble, Time Trade-Off, and Health Utilities Index III.

The EuroQol (EQ-5D) is another instrument for measuring utilities. It is a 2-part questionnaire that takes the patient approximately 5 minutes to complete (Schultz 2002). The first part consists of 5 items covering 5 dimensions, including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problem, 2- moderate problems, and 3-extreme problems. There are 243 potential health states. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm, 10 point-interval scale. Either the index score or the VAS score can be used in the quality-adjusted survival analysis (Wu 2002). The benefit of measuring quality-adjusted survival is that it can be compared to the outcomes of other interventions across disease sites and can be used by health policy makers to rank interventions.

If the primary endpoint is met, the EQ-5D will be used to evaluate the effect of the use of protons as compared to photons on quality-adjusted survival in this trial. Similar to the primary survival endpoint, it is hypothesized that proton RT will be associated with higher quality-adjusted survival as compared to photon RT.

The EQ-5D will be administered at baseline, and then at 1, 3, 6 and 12 months post RT treatment completion. The EQ-5D is also being collected on NRG/RTOG 1112. Patients will be included in the quality adjusted survival analysis only if they have provided both baseline and at least one subsequent measurement.

11.3 Imaging Component

Response to radiotherapy will be assessed using standard 2D (Response Evaluation Criteria for Solid Tumors [RECIST] and European Association for the Study of Liver [EASL]). These will be retrospectively reviewed centrally by the radiology and radiation oncology co-chairs. Additionally, these response criteria will be compared to a 3D assessment of response that has been developed called quantitative EASL (qEASL). The qEASL criteria for liver tumors were originally tested for liver tumors after transarterial chemoembolization (Lin 2012, Chapiro 2014, Duran 2014). Those who responded by qEASL assessment had significantly longer median survival (40.5 months) compared to non-responders (3.6 months, HR=0.00; 95% CI = 0.00-0.34; P<0.001) (Duran 2014). We will extend these results to patients who receive radiotherapy on this trial. Based on the results in (Duran 2014), we conservatively estimate that the hazard ratio (HR) for local failure is 0.45 for responders compared to non-responders by qEASL criteria. To have at least 80% power to detect a difference in local control by qEASL criteria, we would need 60 patients. This estimate assumes an accrual period of 24 months, follow up time of 24 months, and median local control time of 12 months. With a target accrual of 186 patients for this trial, we will be well powered to assess the use of qEASL as a response marker for radiotherapy in HCC.

Submission of imaging will be required on all patients.
The required imaging for each subject is a CT Chest/Abdomen/ Pelvis with Multiphasic Liver CT or CT Chest without contrast and MRI of Abdomen, prior to step 1 registration (30 days), and at end of RT: q3 mos. x 2 yrs.; q6 mos. x 3 years; then annually for up to 5 years, unless otherwise indicated. *(Refer to section 5.2.3 for detail image acquisition parameters)*

For question regarding submission of diagnostic CT exams contact: IROCPHILA-DI@acr.org ***(In the subject line enter NRG-GI003 imaging inquiry)***
Image Submission to IROC using the TRIAD software (also reference section 8.3)
The Image and Radiation Core (IROC) (https://www.irocqa.org/), an NCI funded consortium will support the image collection utilizing the TRIAD software.
Similar to nearly all NCTN clinical trials involving image collection, this trial will use TRIAD software for anonymization and submission of standard of care images to a central archive. Anonymization and submission of standard of care images to a central archive.

TRIAD (Transfer of Images and Data) is a software application that provides secure and essential de-identification of subject PHI and facilitates easy, efficient, and robust transmission of medical images and related electronic data. The TRIAD software is easily downloaded via browser and installed on Windows PCs.

Detailed information including instructions for access to TRIAD, CTEP-IAM Account Registration, TRIAD installation, as well as, user guides can be found at the following link: (https://triadhelp.acr.org/ClinicalTrials/NCISponsoredTrials.aspx).

For Questions about TRIAD installation, contact
TRIAD-Support:
T: 703.390.9858
E: TRIAD-Support@acr.org
The TRIAD Support team is available from Monday to Friday between 8 AM and 5PM EST

12.0 MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

Pre Treatment Reviews
The first photon and proton case from each institution will require a Pre-Treatment Review. Patients cannot start treatment until they have received approval from IROC – Philadelphia RT. The Pre-Treatment Review requires 3 business days from the receipt of complete data.

The Radiation Oncology Co-Chairs, Dr. Hong, Dr. Crane, and Dr. Koay, will perform an RT Quality Assurance Review after IROC-Philadelphia RT has received complete data. These reviews will be completed remotely and be ongoing. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as IROC–Philadelphia RT has received complete data for all cases enrolled, whichever occurs first. The scoring mechanism is: Per Protocol, Acceptable Variation, and Deviation

Unacceptable, based on criteria in Section 5.

13.0 ASSESSMENT OF EFFECT

Definition of Disease Assessments

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

14.0 DATA AND RECORDS

14.1 Data Management/Collection (19-DEC-2025)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read-Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role, must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave resource materials (Medidata Account Activation and Study Invitation). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

14.2 Summary of Data Submission (19-DEC-2025)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.

Summary of all Data Submission: Refer to the protocol-specific page on the CTSU website.

See Section 8 for TRIAD account access and installation instructions. See data submission table for TRIAD below.

Imaging guidelines are provided below as recommendations for the performance of standard-of-care imaging. These guidelines are intended to supplement, not replace, your institutional standard of care imaging parameters.

The Diagnostic Imaging Guidelines are available in the Diagnostic Imaging section of the NRG/CIRO website (https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology/CIRO-Resources).

- CT Abdomen Pelvis
- CT Chest
- MRI Liver Multiphase

DICOM Items	DICOM CT Image	**Due Within 1 week of start of RT.** Triad Time Point: *RT Digital Plan*
	DICOM Structure	
	DICOM Dose	
	DICOM Plan	
All required structures must be labeled per the tables in Sections		

5.2.4	
5.2.5	
Imaging needed for Structure Delineation and RT review: • Planning CT shall include the entire abdomen (including 4DCT as needed), contrast enhanced scans must include the entire liver at a minimum for use for target delineation • For motion management purposes, a 4DCT should be acquired for this study • MR imaging for target delineation is recommended if CT cannot be acquired due to contraindication	
Baseline scan must be submitted with RT data for plan review Multiphasic CT utilizing iodine intravenous (IV) contrast including: 1) Non-contrast CT (planning CT) 2) Contrast-enhanced arterial phase CT – visualization of hypervascularity 3) Contrast-enhanced portal venous phase CT – visualization of vascular thrombi 4) Delayed phase CT – washout of HCC MR imaging recommended if CT cannot be acquired due to contrast allergy. See 5.2.3	Triad Time Point: *Baseline*
Upon submission of the digital data via TRIAD, complete an online	
Digital Data Submission Information Form (DDSI): https://www.irocqa.org/Resources/TRIAD	
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	

DIAGNOSTIC IMAGING REQUIRED FOR SUBMISSION TO TRIAD

CT Chest/Abdomen/ Pelvis with Multiphasic Liver CT or CT Chest without contrast and MRI of Abdomen The same method of assessment and the same imaging technique should be used for all imaging timepoints	TRIAD Timepoints Baseline Follow-Up *(select appropriate timepoint from dropdown in TRIAD submission queue)* Other

NOTE: Please refrain from anonymizing the DICOM header of any imaging exam prior to uploading into the TRIAD application. Custom DICOM editing can exclude an exam from the final analysis, due to the omission of technical data elements. These elements include, but are not limited to, the study date (0008,0020), acquisition date (0008,0022) scanner station name (0008,1010), scanner serial number (0018,1000), patient weight (0010,1030), patient height (0010,1020) and any scan acquisition parameter. TRIAD has been uniquely configured to locate and scrub all PHI from the exam's DICOM header, during the image transfer to ensure the anonymity of our trial patients.

ATTENTION: Imaging PACS systems store all files associated with patient imaging (ex:dose reports, patient questionnaires, etc). TRIAD cannot anonymize the PHI embedded within these files; however, TRIAD does de-identify all PHI within the image metadata. To screen for and remove any potential PHI, outside of the metadata, during the image submission process, please expand all series within the TRIAD Preview Window and deselect any file which may contain PHI before the files are moved to the submission queue. TRIAD Clean Pixel Tool should be utilized for the removal of PHI that has been "burned into" images as part of their acquisition.

Image Submission and Quality Assurance Review

All imaging should be submitted to the IROC Philadelphia Core Laboratory via TRIAD for Image Quality Assurance (IQA) review. Imaging should be submitted within (3) business days to ensure review and feedback from the Core Lab.

When properly configured, TRIAD software de-identifies, encrypts, and performs a lossless compression of the images before they are transferred to the ACR Imaging Core Laboratory. TRIAD, in turn, transfers specific information related to submitted scans, such as scan date and imaging timepoint information, into the Rave database. To ensure that the system-to-system communication is configured properly, please confirm the following prior to submission of image data to TRIAD:

- Please confirm that the specific DICOM tags related to Study Date (0008,0020), Acquisition Date (0008, 0022) and Series Description (0008, 103e) are present and have values, taking care that all date values are formatted YYYYMMDD for DICOM tags 0008, 0020 and 0008, 0022.
    - Ensuring the date is present, accurate and in YYYYMMDD format allows for successful data exchange from TRIAD to Rave
    - Ensuring that the Series Description is present allows for successful data exchange from TRIAD to Rave
- Please refrain from submitting data in zipped or compressed files, as compressed/zipped file format will not transfer information to the Rave database and the submission cannot be tracked for audit purposes.

Image data not formatted properly per the specifications above may not be processed in TRIAD. Follow up with your radiology team or PACS administrator to ensure that all image data is formatted correctly.

Upon image receipt, an Imaging Technologist will perform an IQA review to ensure that all imaging has been submitted in its entirety, the recommended protocol parameters were followed, and the exam is of adequate image quality. In the event that an exam is deemed non-compliant, a Core Lab Imaging Technologist will issue a query within the Medidata Rave data management system. Sites are expected to resolve data queries within (7) business days.

To ensure anonymity of our trial patients, TRIAD is uniquely configured to remove and/or re-identify Protected Health Information (PHI) from image metadata during the image submission

process.

Do not apply any further anonymization to any exam prior to uploading into the TRIAD application.

Essential data which must be preserved includes the study date, scanner station name, scanner serial number and scan acquisition parameters. Any further anonymization prior to submission via TRIAD may exclude an exam from final analysis due to the omission of these important technical elements.

While TRIAD can de-identify all PHI within DICOM image metadata, some files stored in imaging PACS systems may include data that TRIAD cannot anonymize automatically (including patient questionnaires, dose reports, and other electronic records). For these file types:

- Expand all series within the TRIAD Preview Window
- Deselect files which may contain PHI before moving them to the submission queue (these include files such as protocol pages, patient reports, questionnaires, and study orders)
- Prior to submitting, you may also utilize the Clean Pixel Tool within TRIAD to redact any PHI that has been "burned into" images.

Consult with your PACS administrator or contact the IROC Philadelphia Core Laboratory for further information.

14.3 Data Quality Portal (19-DEC-2025)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms. DQP Form Status, and DQP

Reports modules.

14.4 Global Reporting/Monitoring (10-AUG-2022)

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design (19-DEC-2025)

15.1.1 Stratification

Patients will be stratified with respect to Planned Number of RT Fractions (5 vs. 15) and Tumor Vascular Thrombus (Yes vs. No).

15.1.2 Randomization

This study will use a permuted-block randomization with a 1:1 allocation. The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

15.1.3 Total Accrual

Original

167 randomized patients, with a projected 186 patients registered to reach the required number of randomized patients.

Sample Size Reduction

The trial will be closed to accrual after this amendment is approved with a projected randomized accrual of 118 patients.

15.2 Study Endpoints (30-July-2018)

15.2.1 Primary Endpoint

Overall survival

15.2.2 Secondary Endpoints

- Progression-free survival
- Local progression
- Adverse Events evaluated using CTCAE version 5.0
- Patient Reported Outcomes – PROMIS fatigue Short Form v 1.0 8a
- Correlation of HGF biomarker with OS, PFS and fatigue
- Quality adjusted survival (*if primary endpoint is met*)

15.2.3 Exploratory Endpoints

- Patient Reported Outcomes – FACT-Hep v 4

15.3 Primary Objectives Study Design (19-DEC-2025)

15.3.1 Primary Hypothesis and Endpoint

Failure for overall survival (OS) is defined as death due to any cause. It is hypothesized that proton radiation therapy will significantly improve OS, compared to photons, for patients with unresectable or locally recurrent hepatocellular cancer, due to a higher

prescription dose using an effective volume strategy**.**

15.3.2 How Primary Endpoints Will Be Analyzed

OS will be measured from the date of randomization to the date of death due to any cause or date of last follow-up for patients without an OS event reported (censored). OS will be estimated by the Kaplan-Meier method (Kaplan 1958). The distributions of OS between treatment arms will be compared using the log rank test (Mantel 1966).

Analysis for Reporting the Initial Treatment Results

The final analysis will occur after at least 88 deaths have occurred or 48 months after accrual closure, whichever occurs first. The analysis will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- treatment delivery compliance
- observed results with respect to the primary endpoint of OS

All eligible patients randomized will be included and will be grouped by randomized treatment in the analysis. With an overall 1-sided alpha=0.05, the primary hypothesis of improved OS, assuming the interim analysis has been carried out, will be tested with a 1-sided significance level of 0.039. If the p-value for the log-rank test statistic comparing treatments is ≤ 0.039, in favor of protons, it will be concluded that OS is improved with protons vs photons. Additional analyses of treatment effect will be performed using the Cox proportional hazard regression model (Cox 1972) with the stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms (e.g. age, gender, race, etc.). Where feasible, treatment comparisons with respect to the primary endpoint (OS) will be compared within each ethnic and racial category.

15.3.3 Sample Size and Power Calculations:

Original

The null hypothesis is that there is no difference in OS between the treatment arms. The alternative hypothesis is that there is a difference in OS. Median OS on the photon arm is estimated to be 14 months based on the range of 10-15 months reported for HCC patients with vascular tumor thrombus treated with radiation alone. As the protocol population will include patients treated with 5 or 15 fractions, the photon arm estimate of median OS is consistent with the 17 months reported for SBRT at a single institution (Bujold 2013) and with the 14.5 months hypothesized on the combination arm of SBRT and sorafenib in the ongoing NRG/RTOG 1112 protocol. Median OS on the proton arm is hypothesized to be 24 months (hazard ratio = 0.58) based on the recently completed phase II protocol DF/HCC 09-131 (Hong 2015) that showed 2-year OS of 71% using a 15-fraction schedule of protons.

A total of 155 evaluable patients, using a group sequential design with one interim analysis, will provide the 125 OS events (deaths) for 85% power to detect the

hypothesized difference, using a log-rank test at a two-sided 0.05 alpha level. Guarding against ineligibility or lack-of-data rate of up to 7%, the targeted accrual of randomized patients for this study will be 167 patients. It is projected that up to 186 patients will need to be registered to reach the required number of randomized patients.

Sample Size Reduction
The statistical design/analysis plan changes were done in accordance with the NCI Policy for Major Design Amendments for Ongoing Randomized Clinical Trials. The specifics for the changes were performed by a statistician independent from the trial.

Based on recommendations from the NRG Oncology Data Monitoring Committee and concurrence by NCI and the NRG investigators, accrual will close after this amendment is approved, with an anticipated 118 randomized patients. Based on observed ineligibility/loss rates, the effective sample size is projected to be 112 patients.

To accommodate the reduced sample size, specific changes are required to maintain the primary study objective. The original effect size (HR = 0.58) will be maintained while the power will be reduced to 80% and the type I error rate modified to one-sided 0.05. The definitive analysis will require observation of 88 OS events. Factoring in the moderately more favorable control (photon) group failure rate than originally assumed, the requisite OS events are projected to be observed within 48 months from accrual closure.

15.3.4 Study Monitoring of Primary Objectives

Interim Reports to Monitor the Study Progress
Interim reports with will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pre-treatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, OS, or any secondary endpoints, with the exception of reporting of adverse events.

Significance Testing for Early Termination and/or Reporting
Primary Endpoint: Overall Survival (OS)
One interim significance test of treatment effect for the primary endpoint of OS is planned based on the Lan DeMets alpha/beta spending functions (Lan 1983) and will be done when 53 (60%) of the required 88 OS events have occurred. The standard Weiand rule will be used for futility. The boundaries for rejecting the null hypothesis and concluding futility at the interim analysis are shown in the table below:

Table 1: Nominal Significance Level for Interim Analyses

Interim Analysis	Number of Events	Reject H_0 if $p \leq$	Conclude Futility
#1	63	≤ 0.011	HR(protons/photons) > 1

At the planned interim analysis, the results from testing the H_0 for OS will be compared to the boundary level in Table 1 above. If the boundary to reject H_0 and/or conclude futility is crossed, then recommendations will be made to the NRG DMC relative to stopping accrual (if applicable) and/or reporting the study results early, otherwise, accrual to the trial and/or follow-up (as applicable) will continue until the final analysis.

In addition to the routine reporting of accrual, distributions of pretreatment characteristics, and frequency/severity of adverse events, the interim efficacy/futility results will be reported to the NRG Oncology DMC, following the required number of events for the planned interim analysis.

DMC Reviews
The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study for the protocol-specified primary endpoint interim analysis, as well as on an "as needed" basis for any other issues.

CDUS Reporting
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

15.3.5 Accrual/Study Duration Considerations

Original

Patient accrual is projected to be 3.5 randomized cases per month with a ramp-up period of little to no accrual expected in the first three to 6 months, and will be completed in just over 4 years. Assessment of accrual compliance will be based on the NCI Phase III accrual rules and will be monitored by the NRG Oncology Data Monitoring Committee (DMC). It is projected that 12 months of follow-up, after accrual is completed, will be necessary to reach the required 125 OS events.

Sample Size Reduction

Under the sample size reduction, accrual will be completed in 8.5 years from activation. Follow-up time to trigger primary endpoint analysis will be the time to reach 88 OS events or 48 months after accrual closure, whichever occurs first, such that maximum duration from activation to primary endpoint analysis will be 12.5 years.

15.4 Secondary/Exploratory Endpoints (19-DEC-2025)

15.4.1 Secondary Endpoints:

- Progression-free-survival (PFS) (*failure: local/regional/distant progression or death due to any cause*)
- Local progression (LP) (*failure: local progression*)

- Adverse events (per CTCAE version 5.0)
- Fatigue measured by PROMIS Fatigue Short Form v 1.0 8a
- Quality-adjusted survival using EQ-5D (*only if primary endpoint is met*)
- Correlation of HGF biomarker with OS, PFS, and fatigue

15.4.2 Exploratory Endpoints

- QOL measured by FACT-Hep v 4

15.4.3 Definitions of Secondary/Exploratory Endpoints and How These Will Be Analyzed

Efficacy Endpoints

Progression-free survival (PFS) is defined as local/regional/distant progression or death due to any cause and will be estimated by the Kaplan-Meier method (Kaplan 1958). The distribution of PFS estimates between the two arms will be compared using the log rank test (Mantel 1966). PFS time will be measured from the date of randomization to the date of first PFS failure or last follow-up for patients without a reported PFS event (censored). The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, which may be associated with DFS (Cox 1972).

Local progression (LP) will be estimated by the cumulative incidence method (Kalbfleish 1980). The distribution of LP estimates between the two arms will be compared using Gray's test (Gray 1988). LP time will be measured from the date of randomization to the date of first LP or date of last follow-up for patients without an LP event reported (censored). The Fine-Gray regression model will be used to analyze the effects of factors, in addition to treatment, which may be associated with LP (Fine 1999).

Adverse Events

Adverse events (AEs) will be graded as described in Section 7.2.1 and presented in statistical analysis reports/publications in CTCAE version 5.0. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. A Chi-square test will be used to compare the number of patients with at least 1 grade 3 or higher AE between the treatment arms.

Patient Reported Outcomes (PRO/ Quality of Life (QOL)

Fatigue

Fatigue, as measured by the PROMIS Fatigue Short Form v 1.0 8a, will be the primary PRO/QOL endpoint and will be collected at baseline and then at 1 and 6 months post radiation treatment completion. The primary hypothesis is that patients treated with proton radiation therapy will have significantly less patient reported fatigue at 1 month post treatment completion as compared to patients treated with photon radiation therapy. With a 2-sided alpha of 0.05, the study sample size of 118 patients will provide 68%, 77%, 80% and 84% power to detect 0.45, 0.50, 0.52, and 0.55 standard deviation effect sizes, respectively.

Change (1 month score – baseline score) in fatigue will be compared between treatment arms using a t-test. If the data do not satisfy the normality assumption, a Wilcoxin test

may be used instead.

Overall QOL

QOL will be measured by the FACT-Hep v 4 and will be collected at baseline and then at 1, 3, 6, and 12 months post radiation treatment completion. The primary hypothesis is that more patients treated with proton radiation therapy will have an improved overall QOL at 6 months post treatment completion as compared to patients treated with photon radiation therapy. Improvement is defined as an increase in the FACT-Hep score of at least 5 points (minimally important difference) from baseline to 6 months. Differences between treatment arms in the overall score, the four domains (physical, social, emotional, and functional well-being), and the additional concerns subscale will also be analyzed.

Quality-adjusted survival

The quality-adjusted survival of each treatment will be evaluated and compared using EQ-5D if the primary endpoint supports the primary hypothesis.

The EQ-5D is a 2-part self-assessment questionnaire. The first part consists of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point likert scale (1-no problems, 2-moderate problems, and 3-extreme problems). The second part is a visual analog scale (VAS) valuing the current health state measured by a 100-point scale with a 10-point interval (0-worst imaginable health state, 100-best imaginable health state). The 5-item index score and VAS score will be transformed into a utility score between 0 (worst health state) and 1 (best health state) for comparative purposes. Patients will complete the EQ-5D at the following time points: pretreatment (baseline), 1 month, 3 months, 6 months, and 12 months post treatment completion.

To examine trade-offs between the survival time and QOL, they will be combined for each patient into a single measurement: quality-adjusted life years (QALY). If (and only if) the primary endpoint hypothesis is substantiated, a quality-adjusted survival analysis will be conducted. The quality-adjusted survival analysis will not be done until after the primary endpoint results are published. QALY is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. QALY will be analyzed initially at 6 and 12 months from treatment completion, using the EQ-5D. QALY may also be analyzed at 1 and 3 months, depending on differences in QOL at those time points.

Missing Data

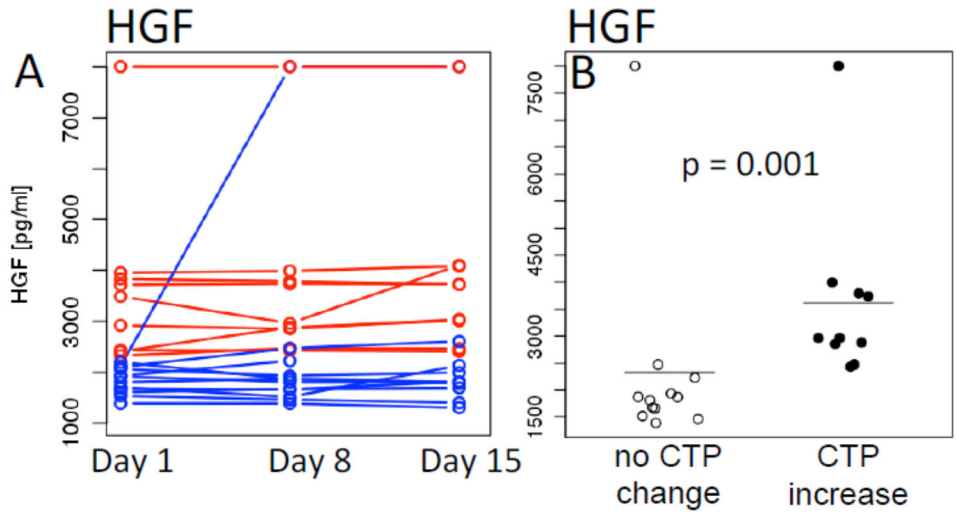
Distributions of QOL data collection patterns over all collection points in each treatment arm will be described. To inspect the missing data mechanism for each tool, at least a graphical method will be used. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples.

If the missing data is MCAR, list-wise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data.

If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline QOL score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism (Donaldson 2005) and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the complete case analysis results to assess any potential biases**.**

15.5 Translational Research (19-DEC-2025)

The correlative science endpoint is focused on evaluating the baseline prognostic significance of plasma HGF levels, with the primary hypothesis that high plasma HGF levels are associated with worse OS. Per a more recent analysis, a cut off of 2311 pg/mL will be used. As seen in the below graph from analyzing the MGH/MDACC study, no patients with HGF below 2311 pg/mL had CTP increase, and vast majority the hepatic dysfunction events defined as CTP increase occurred in patients above 2311 pg/mL.



HGF will be dichotomized at 2311 pg/mL and evaluated for prognostic significance using Cox regression model at a 2-sided significance level of 0.05. The study primary endpoint analysis will occur after 88 OS events or 4 years of follow-up post accrual closure, whichever occurs first. Power information to detect the listed PFS hazard ratios (HR) given the specified number of PFS events is shown in the table below:

	Number of PFS Events			
HR	**90**	**95**	**100**	**110**
2.0	90%	92%	93%	94%
1.9	86%	87%	89%	92%
1.8	79%	81%	83%	86%
1.7	71%	73%	75%	79%

Depending on the distribution of the HGF, analyses as a continuous variable may also be done.

Additionally, predictive analyses will be done by treatment arm and an exploratory test of HGF by treatment interaction, with the understanding that there will be reduced power for the predictive analyses under the same effect size assumptions. However, there may be sufficient power if there is large interaction.

15.6 Other Pre-specified Outcomes: NIH Required Analyses for Trials with Phase III Components (19-DEC-2025)

Estimates of treatment effect and the corresponding 95% confidence intervals (CIs) will be provided as follows (with an understanding that sometimes the CI or estimate will not be computable because of scant data).

- Estimates of the primary outcome treatment effect and the corresponding 95% confidence intervals (CIs) by sex.
- Estimates of the primary outcome treatment effect and the corresponding 95% confidence intervals (CIs) by race.

  Estimates of the primary outcome treatment effect and the corresponding 95% confidence intervals (CIs) by ethnicity.

15.7 Sex/Ethnicity/Race Distribution (19-DEC-2025)

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	7	28	0	0	35
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	1	3
White	9	43	1	1	54
More Than One Race	0	0	0	0	0
Total	17	72	1	2	92

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	2	9	0	0	11
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	1	0	0	1
White	4	10	0	0	14
More Than One Race	0	0	0	0	0
Total	6	20	0	0	26

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APPENDIX I
Child Pugh Classification of Liver Function

Clinical and Biochemical Parameters	Score (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy	None	1 - 2	3 - 4
Ascites	None	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
INR*	< 1.7	1.7 - 2.3	> 2.3
Bilirubin (mg/dL)	1 - 2	2 - 3	> 3

Class A	5 - 6 points
Class B	7 - 9 points
Class C	10 - 15 points

Alternative Biochemical Units	Score (Points) for Increasing Abnormality		
	1	2	3
Albumin (g/L)	> 35	28- 25	< 28
Bilirubin (umol/L)	0-34.2	34.3 - 51.3	> 51.3

Stages of Hepatic Encephalopathy	
Stage 1	Euphoria or depression, mild confusion, slurred speech, disordered sleep
Stage 2	Lethargy, moderate confusion
Stage 3	Marked confusion, incoherent speech, sleeping but arousable
Stage 4	Coma

* INR = International Normalized Ratio for Prothrombin Time

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