Study Title:	A Pilot Study to Assess Feasibility of Hypofractionation and Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma Patients Awaiting Liver Transplantation
Protocol Number:	18810
ClinicalTrials.gov ID:	NCT03812289
Investigational modality:	Hypofractionation and Stereotactic Body Radiation Therapy
Version Number:	1.4
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SUMMARY OF CHANGES

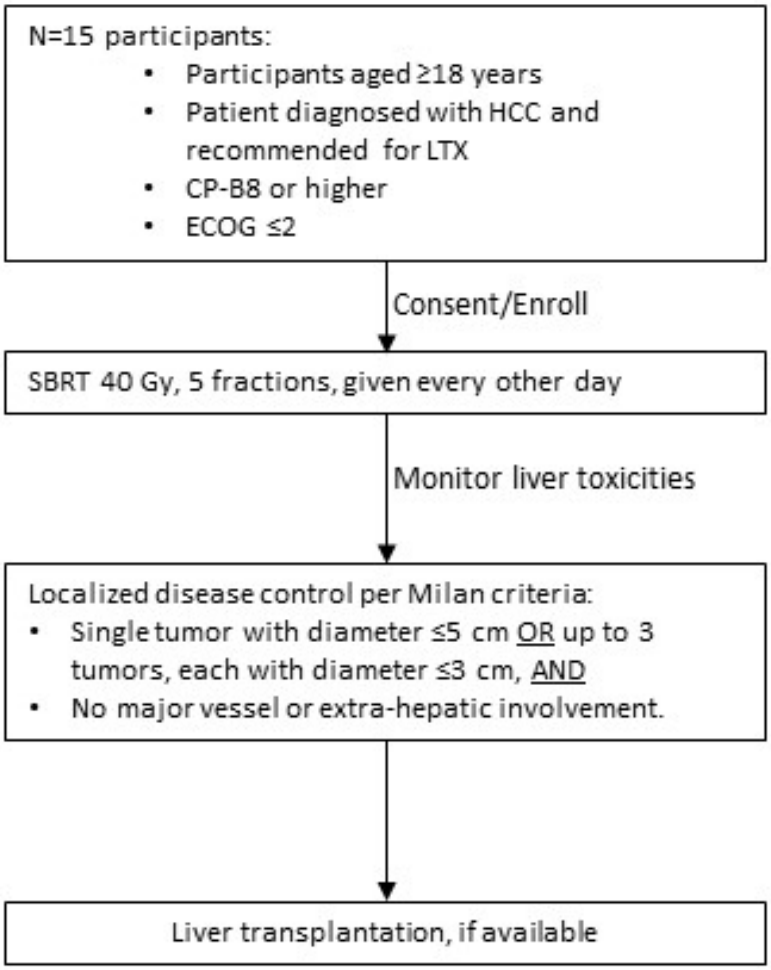
#	Section	Page(s)	Change	Justification
1.	1.2.1	16	Corrected sentence	Previously incomplete
2.	4.5	24	Screening period changed from 10 days to 28 days	Clarified to reflect schedule of events
3.	5.3.1	28	Clarified required duration of contraception after treatment	Inconsistency between exclusion criteria and description in 5.3.1
4.	6.2.2	32	Removed LDH and magnesium from biochemistry panels	These are not part of normal lab panels and are not routinely collected
5.	6.8	34	Updated schedule of events per standard of care	Labs and time points were not represented accurately
6.	Title Page	1	Updated list of investigators and statistician	Include only investigators who are participating in the study and have received training/delegation from PI

SYNOPSIS

Study Title	A pilot study to assess feasibility of stereotactic body radiation therapy for hepatocellular carcinoma patients awaiting liver transplantation
Protocol #	18810
Study Center	OHSU, single-site
Clinical Phase	Pilot
Investigational Component(s)	Radiation Therapy
Interventional Study Type	*Single-arm*
Précis	Liver transplantation (LTX) is the best treatment for patients with hepatocellular carcinoma (HCC) and Child-Pugh (CP) B or C cirrhosis, as both conditions can be very effectively treated at once. As liver transplantation wait-lists can be many months, liver directed therapies (LDTs) are essential as oncologic temporizing measures to bridge patients to transplantation. However, due to the fear of further hepatic decompensation, many patients with advanced cirrhosis are excluded from receiving LDTs. This study hypothesizes that liver stereotactic body radiation therapy (SBRT) can be of safe and practical use in this fragile patient population and may result in the reduction of transplantation drop-out rates. The overall goal of this pilot proposal is to evaluate the feasibility of bridge-to-transplantation liver SBRT in hepatocellular carcinoma patients with Child-Pugh B8 or higher cirrhosis.
Primary Objectives	Assess the use of SBRT in HCC patients with advanced liver cirrhosis as a feasible approach to providing localized disease control that adequately suffices liver transplant eligibility criteria.
Secondary Objectives	Assess preliminary efficacy and toxicity in HCC patients with advanced cirrhosis following liver SBRT
Exploratory Objectives	Assess quality of life (QoL) in HCC patients with advanced cirrhosis following liver SBRT Examine SBRT-related histopathologic changes in explanted livers of patients with advanced cirrhosis.
Primary Endpoints	1. Proportion of participants that are transplant eligible 1 year following SBRT
Secondary Endpoints	1. Incidence of progressive disease within or at the planned tumor volume (PTV) margin (i.e. local control) 2. Incidence of progressive disease within any section of the liver, including the PTV (e.g. intrahepatic disease free survival) 3. Incidence of progressive disease outside of the liver (e.g. extrahepatic disease free survival) 4. Overall Survival 5. Proportion of participants that proceed to transplantation 6. Incidence of non-classical radiation-induced liver disease (RILD), defined as grade 4 aspartate aminotransferase or alanine aminotransferase elevation, or an increase in CP score of ≥ 2 within 1 week to 3 months after completing SBRT.

	7. Incidence of liver toxicity per CTCAE v5.0 within 1 week to 3 months after completing SBRT.
Exploratory Endpoints	1. QoL scores for EORTC QLQ-C30 questionnaire 2. QoL scores for Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire 3. At time of transplantation, histopathologic changes in irradiated tumor sites relative to uninvolved liver tissue will be assessed
Number of Participants	15
Duration of Therapy	SBRT will be administered as 5 fractions every other day (~10 day)
Duration of Follow Up	Time of progression, or transplantation, or 2-years after last SBRT dose, whichever occurs first
Key Inclusion Criteria	1. Participants aged ≥18 years 2. Patient diagnosed with HCC and recommended for LTX 3. Meets clinical criteria for eligibility for SBRT to the target lesion 4. Childs-Pugh Class B8 or higher 5. Eastern Clinical Oncology Group performance status ≤2 6. Safe radiation treatment planning parameters that adhere to all organs at risk constraints per section 5.1 of the protocol. If normal organs at risk constraints (including at least 700cc of uninvolved liver) are unable to be met at the lowest dose modification (30 Gy in 5 fractions), the patient is deemed ineligible for SBRT and deemed a screen failure.
Key Exclusion Criteria	1. Prior radiotherapy to the upper abdomen or radioembolization of the liver 2. Prior SBRT to the target lesion, RFA, or LTX 3. Active GI bleed within 2 weeks of study enrollment 4. Contraindication to receiving SBRT 5. Contraindication to both contrast enhanced MRI and contrast enhanced CT (i.e. unable to undergo follow-up imaging or SBRT treatment planning) 6. Women who are pregnant
Investigational Product	SBRT
Statistical Considerations	This is a pilot study with no formal hypothesis test but to assess a preliminary estimate of feasibility. A sample size of 15 patients will ensure that at least on 1 SBRT ineligible participant is encountered (at a 95% confidence interval).

SCHEMATIC OF STUDY DESIGN



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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CHO	Community Hematology & Oncology
CFR	United States Code of Federal Regulations
CP	Child-Pugh criteria
CR	Complete response
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CSF	Cerebral spinal fluid
CT	Computerized tomography
CTEP	Cancer Therapy Evaluation Program
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	Disease-free survival
DLT	Dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LDT	Liver directed therapy
LFT	Liver function test
LTX	Liver transplantation
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable
NCI	National Cancer Institute
OHRP	Office for Human Research Protections

OHSU	Oregon Health & Science University
PD	Progressive Disease
PET	Positron emission tomography
PI	Principle Investigator
PR	Partial response
QOL	Quality of Life
RBC	Red blood cell (count)
RILD	Radiation-induced liver disease
RNI	Reportable new information
RT	Radiation therapy
SAE	Serious adverse event
SBRT	Stereotactic body radiotherapy
SD	Stable disease
SD	Standard deviation
TAE/TACE	Transarterial embolization / transarterial chemoembolization
TSMP	Trial Specific Monitoring Plan
ULN	Upper limit of normal
UP	Unanticipated problem
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) accounts for 90% of liver cancers worldwide, with an approximately 782,000 new cases and 746,000 deaths expected in 2012.[1] In the United States alone, HCC is attributed to nearly 30,000 deaths annually.[2,3] The age-adjusted worldwide incidence of HCC is 10.1 cases per 100 000 person-years, and this number is expected to continue rising as the number of hepatitis C virus (HCV) carriers increases.[4]

Partial hepatectomy or LTX are the only available curative treatments; however, >80% of patients with HCC have chronic liver disease, and mandatory hepatic reserve requirements often exclude many patients with advanced cirrhosis from liver resection. In patients with early to intermediate-stage HCC and advanced liver disease, LTX confers superior disease-free survival compared to resection.[5] Whether a patient is eligible for LTX is largely based on the Milan selection criteria established by Mazzaferro et al[6], which demonstrated that LTX recipients with early HCC (as defined by having either a single lesion no > 5 cm or ≤ 3 lesions each ≤ 3 cm) can achieve favorable long term patient survival. Unfortunately, prolonged wait times pose a major disadvantage to patients awaiting suitable livers.[7,8] Rather, using these criteria, 20-30% of listed patients will have oncologic progression outside of the Milan criteria during this waiting period.[9] To minimize the risks of disease progression, a bridge-to-LTX using LDT is often recommended.[10] Whereas ideal candidates for LDT have preserved liver functions with Child-Turcotte-Pugh (CP) scores of B7 or better[11], many LTX candidates with advanced cirrhosis (CP-B8 or higher) are excluded from treatment as they lack sufficient hepatic reserve.

1.2 LIVER DIRECTED THERAPIES

Alternative therapeutic approaches to LTX for patients with unresectable HCC include, partial hepatectomy, radiofrequency ablation, transarterial embolization/chemoembolization (TAE/TACE), and radioembolization, among others.[12] Unfortunately, many of these approaches are associated with procedural complications that can cause significant morbidity.

TACE with the transcatheter delivery of a mixture of chemotherapy and embolic agents is considered standard of care for early and intermediate stage unresectable HCC patients with preserved liver function.[12] This approach is associated with a strong response rate (OR: 5.95; 95%CI: 2.96–11.99), and is significant survival benefit over best supportive therapy (HR: 0.76; 95%CI: 0.64–0.91).[13] However, major complications associated with this approach include (but are not limit to): hepatic failure, liver abscess, liver rupture, biliary tract injury, renal failure, necrotizing pancreatitis, cerebral lipiodol embolism, and hepatic encephalopathy.[14-16] Aside from complications, use of TACE is also limited by cases of excessive tumor burden (i.e., <50% of liver) and minimum tumor size (i.e., >5 cm) requirements, as well as limitations of vascular invasion, biliary obstruction, and anatomical localization (e.g., infradiaphragmatic or adjacent to large vessels). Moreover, TACE, is generally not performed for patients having Child-Pugh classification C (or late B); further highlighting the limited treatment option for patients with severely compromised liver function.

1.2.1 STEREOTACTIC BODY RADIOTHERAPY OF LIVER IN SETTING OF ADVANCED CIRRHOSIS

Guidelines have historically omitted external beam radiation therapy for the management of HCC because of the high incidence of radiation-induced liver disease (RILD). Modern advances to computer and imaging technologies have greatly improved methods of conformal

liver irradiation, which are associated with RILD ≤ 5%.[17] SBRT involves the use of a few (≤10) potent doses of highly conformal radiation therapy with high geometric precision and accuracy.[18] These advances have renewed interest in SBRT as an approach to managing HCC, with data from several studies supporting its safety and efficacy in patients with the greatest degree of hepatic reserve.[19-22]

Bujold et al[19] reported on the outcomes of a prospective trials consisting of 102 evaluable patients with HCC (CP-A) that were treated with SBRT. The underlying liver disease among patients consisted of hepatitis B (38%), hepatitis C (38%), alcohol related (25%), other disease (14%), and no disease (7%). The authors evaluated patients 1-year after receiving SBRT (dose range: 24 to 54 Gy in six fractions), and observed local control of 87%, and a median overall survival of 17 months. Toxicity ≥ grade 3 was reported in 30% of patients. Importantly, no RILD was observed.

Lasley et al[20] conducted a phase 1-2 trial to examine variables influencing liver toxicity in patients receiving SBRT for hepatocellular carcinoma. In this study, 38 CP-A (39 lesions) and 21 CP-B (26 lesions) patients were followed for ≥6 months following SBRT. The authors observed that local control at 6 months was 92% for CP-A and 93% for CP-B. Two- and 3-year estimates with local control was 91% for CP-A and 82% for CP-B (P = .61). The median overall survival was 44.8 months and 17.0 months for CP-A and CP-B. Assessment of safety among CP-A and CP-B patients revealed 4 (11%) and 8 (38%) patients that experienced grade III/IV liver toxicity, respectively. The authors further reported that the risk of death was 4.6 times greater for CP-A patients with ≥grade III liver toxicity compared to those without toxicity. In contrast, no such correlation was seen for CP-B patients. Notably, CP-B patients experiencing grade III/IV liver toxicity had significantly higher mean liver dose, higher dose to one-third normal liver, and larger volumes of liver receiving doses <2.5 to 15 Gy in 2.5-Gy increments. This finding suggests that for CP-B patients, careful consideration should be given to low-dose volumes that could potentially result in increased liver toxicity. Overall, the authors concluded that SBRT is safe for therapy of patients with HCC.

In a recent retrospective study, Nabavizadeh et al[22] reported on their single institution experience using SBRT or hypofractionated radiation therapy (AHRT) to treat 146 HCC patients with varying degrees of cirrhosis. The cohort included 51 patients with CP-B8 or higher cirrhosis (34% of entire cohort). Within this cohort, only a third of all patients experienced toxicity, defined as a CP elevation of 2 or more within 6 months of RT. These findings are comparable with other reports.[20,21] Notably, the authors did not identify a statistically significant difference between rates of toxicity when comparing patients with CP-B8 or higher baseline cirrhosis to those with CP-A or B7 cirrhosis. Thirteen patients in the cohort with CP-B8 or higher cirrhosis eventually underwent LTX; suggesting that radiotherapy affords localized disease control for these patients awaiting transplantation. In this regard, the authors further observed that the 1- and 2-year local control (LC) rates were greater significantly better among patients receiving SBRT compared to those given AHRT (1-year LC 97% vs 72%, P <.0001; 2-year LC 94% vs 65%, P <.0001).

1.3 **RATIONALE**

Liver transplantation (LTx) is the best treatment for patients with hepatocellular carcinoma HCC and CP-B or C cirrhosis, as both conditions can be very effectively treated at once. As LTX wait-lists can be many months, LDTs are essential as oncologic temporizing measures to bridge patients to LTX. However, due to the fear of further hepatic decompensation, many patients with advanced cirrhosis are excluded from receiving LDT. Rather, recent studies suggest that SBRT can be of safe and practical use in this fragile patient population, and thereby reduce the rate of transplantation drop-out.[22,23]

In this pilot study of HCC patients with severe cirrhosis, the feasibility of utilizing SBRT will be evaluated as a stopgap method to provide localized disease control until time of transplantation. By achieving the study endpoints listed in Section 3.2, this pilot trial will contribute to the development of a larger-scaled multi-institutional clinical trial of SBRT in HCC patients with advanced hepatic decompensation by sharpening our hypothesis, identifying barriers to subsequent study participation and estimating bridging efficacy relative to historical controls.

1.4 **POTENTIAL RISKS AND BENEFITS**

1.4.1 KNOWN POTENTIAL RISKS

The use of SBRT is associated with increased risk for radiation-induced liver disease and further decompensation of liver function. At Oregon Health and Science University, the treatment of patient with severely compromised liver function is associated with a 31% increase in liver toxicity, as determined by an increase CP score of ≥ 2 within 6 months after SBRT.[22] Only 11 of 146 patients (7.5%) were observed to have a Grade 4 toxicities (per Common Terminology Criteria for Adverse Event [CTCAE] criteria) within 6 months of RT. These grade 4 AEs consisted of 1 gall bladder perforation, 4 cases of thrombocytopenia, 2 cases of hyperbilirubinemia, 2 cases of upper gastrointestinal bleeding, and 2 cases of encephalopathy; however, no definitive treatment-related deaths were seen. In comparison, authors of a separate institutional study observed that 26% of 101 patients with baseline CP-A cirrhosis and 7 of 13 (53%) of patients with CP-B7 cirrhosis experienced CP ≥ 2 toxicity within 3 months of 6-fraction SBRT.[24] However, it is very challenging to discern treatment-related hepatic toxicity from natural decline of hepatic functionality secondary to advanced cirrhosis. For example, the SHARP trial, a randomization of placebo versus sorafenib for advanced HCC, identified that the placebo arm had a 52% rate of adverse events likely due to cirrhosis or HCC progression.[25] Refer to Section 8.4 for additional information.

1.4.2 KNOWN POTENTIAL BENEFITS

There are a minimal number of approaches currently available to help bridge the time to transplantation in patients with severely compromised liver function. The current study using SBRT may provide access to a new treatment approach not previously available. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

Assess the use of SBRT in HCC patients with advanced liver cirrhosis as a feasible approach to providing localized disease control that adequately suffices liver transplant eligibility criteria.

2.2 SECONDARY OBJECTIVES

Assess preliminary efficacy and toxicity in HCC patients with advanced cirrhosis following liver SBRT.

2.3 EXPLORATORY OBJECTIVES

Assess qualify of life in HCC patients with advanced cirrhosis following liver SBRT. Examine SBRT-related histopathologic changes in explanted livers of patients with advanced cirrhosis.

3. STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 9*, Statistical Considerations, for additional information regarding statistical methods used in this study.*

This is pilot study to assess the feasibility of bridge-to-transplantation SBRT for patients with severe liver disease. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

In general, patients with CP-B8 or higher cirrhosis and non-metastatic HCC who have been listed or recommended to be listed for liver transplantation will be eligible for participation in this study. Eligible participants will undergo SBRT consisting of 40 Gy to be given in 5 fractions every other day provided that criteria for normal organ constraints are met (i.e., ≥700 cc of uninvolved liver). In cases where normal organ constraints are not met, the dose will be iteratively de-escalated to two dose levels (35 Gy in 5 fractions, then 30 Gy in 5 fractions). If normal organ constraints are unable to be met at 30 Gy in 5 fractions, the participant will be considered ineligible for SBRT and considered a screen failure.

Following SBRT, the rate of radiation-induced liver disease (non-classical RILD) and associated toxicities will be evaluated, along with treatment response and an assessment of quality of life associated with SBRT. The proportion of participants that are successfully bridged to liver transplantation, and times to liver transplantation following SBRT will be recorded for each participant. Additional exploratory studies will assess SBRT-related histopathologic changes in explanted livers of participants with advanced cirrhosis. In these studies, pathologic treatment response in explanted livers will be evaluated, and regions of uninvolved liver both near and remote to the irradiated volume will be assessed for histopathologic changes consistent with RILD (e.g., obliteration of central veins, increased perisinusoidal reticulin network and hepatocyte necrosis).

This study aims to enroll 15 participants at OHSU. Participant data for primary, secondary, and exploratory endpoints will be collected by the site providing clinical care. The analyses of the data collected will take place at OHSU.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT

Endpoint	**Start**	**End**
Proportion of participants who are transplanted or with localized disease control that meets Milan criteria (Section 7.5) within 1 year	Start of SBRT	Time of progression, or transplantation, or 1-years after last SBRT dose, whichever occurs first

3.2.2 SECONDARY ENDPOINTS

Endpoint	Start	End
1. Localized control rate: Incidence of progressive disease within or at the planned tumor volume (PTV) margin	First dose of SBRT	Time of progression, transplantation, death or 2-years after last SBRT dose, whichever occurs first.
2. Incidence of intrahepatic progressive disease		
3. Incidence of extrahepatic progressive disease		
4. Proportion of participants that proceed to transplantation		
5. Overall Survival		Time of death or 2-years after last SBRT dose
6. Incidence of non-classic RILD, defined as grade 4 aspartate aminotransferase or alanine aminotransferase elevation, or an increase in CP score of ≥ 2 within 1 week to 3 months after completing SBRT (Appendix A)		3 months after last SBRT dose

3.2.3 EXPLORATORY ENDPOINT

Endpoint	Start	End
QoL scores for QLQ-C30 questionnaire	Screening	Death or 2-years after last SBRT dose, whichever occurs first
QoL scores for Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire		
Proportion of histopathologic changes in irradiated tumor sites relative to uninvolved liver tissue	Transplantation	Transplantation

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to understand and the willingness to sign a written informed consent document.
2. Age ≥18 years at time of informed consent. All people regardless of biologic sex and members of all races and ethnic groups will be included.
3. Must be listed or recommended to be listed for orthotopic liver transplantation at the participating institution
4. Have a CP score ≥ B8, as defined in Appendix A
5. Eastern Clinical Oncology Group (ECOG) performance status ≤ 2, or Karnofsky Performance Scale >60 (refer to Appendix B)
6. Must have a life expectancy > 12 weeks
7. Safe radiation treatment planning parameters that adhere to all organs at risk constraints per section 5.1 of the protocol. If normal organs at risk constraints (including at least 700cc of uninvolved liver) are unable to be met at the lowest dose modification (30 Gy in 5 fractions), the patient is deemed ineligible for SBRT and deemed a screen failure.
8. Except for prior radiotherapy or radioembolization, other prior therapies to previously treated lesions, are permitted.
9. People of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of SBRT. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year without an alternative medical cause.

   Note: Abstinence is acceptable if this is the preferred contraception for the participant.
10. No other prior invasive malignancy is allowed except for the following: adequately treated basal (or squamous cell) skin cancer, in situ breast or cervical cancer. Stage I or II invasive cancer treated with a curative intent without evidence of disease recurrence for at least five years.

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Participants have any one of the following liver tumor characteristics:
   a. have > 5 liver tumors, or
   b. maximal diameter > 5 cm
2. Complete obstruction of portal venous flow to the segment of liver that includes the target lesion
3. Prior radiotherapy to the upper abdomen or radioembolization of the liver, or prior thermal

ablation to the target lesion.

4. For fiducial marker placement:
    a. Have a gold allergy,
    b. Any coagulopathy preventing safe fiducial placement
5. Contraindication to both contrast enhanced MRI and contrast enhanced CT (i.e. unable to undergo follow-up imaging or SBRT treatment planning)
6. Participation in another concurrent treatment protocol
7. Participant is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
8. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants for this study will primarily be recruited from hematology and oncology practices within OHSU and its affiliated community hematology and oncology (CHO) practices. Participants may also be identified and referred to this study by their primary treating physician from within OHSU, CHO, VAPORHCS, or from the outside community. Participants may be identified by a member of the patient's treatment team, the PI, research team, or medical and surgical oncology clinics part of OHSU, CHO, or VAPORHCS. As a member of the treatment team, the investigator(s) will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study, which may include discussion of patient at a multidisciplinary liver tumor board meeting. In these meetings, a participant's medical history will be presented at a multidisciplinary comprised of hepatobiliary surgical oncologists, medical oncologists, radiologist, radiation oncologists, and hepatologists. In this conference, patient imaging and pathology may be reviewed by the group for consensus that the prospective participant satisfies all inclusion and exclusion criteria. Referral of potential participants to investigator(s) of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of the patient's malignancy.

The investigators(s) may also screen the medical records of potential participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of participating in the study. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

4.3.1 ACCRUAL ESTIMATES

The number of participants to be accrued is driven by the study primary objective. An estimated 15 participants over a 12 month period.

This study will not focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited. Male, female and minority volunteers will be recruited for this study from the general population. The incidence of male HCC is disproportionately higher than females; at a rate of approximately 2:1 across studies reported.[4] The projected gender, racial, and ethnic composition of the study, adjusted for the approximate 2:1 disproportion in male to females, will otherwise represent that of the state of Oregon (**Table 1**).

Table 1. Projected accrual for present study based on Oregon population demographics

Ethnic Category [OR]	**Sex/Gender**					
	Females		Males		Total	
	n	*%*	n	*%*	n	*%*
Hispanic or Latino	0-1	*6.5*	1-2	*6.3*	2	*12.8*
Not Hispanic or Latino	3	*44.0*	9	*43.2*	12	*87.2*
Ethnic Category: Total of all participants*	4		11		15	*100**
Racial Category						
American Indian or Alaskan Native	0	*0.9*	0	*0.9*	0	*1.8*
Asian	0	*2.3*	0-1	*2.2*	1	*4.5*
Black or African American	0	*1.1*	0	*1.0*	0	*2.1*
Native Hawaiian or other Pacific Islander	0	*0.2*	0	*0.2*	0	*0.4*
White	3	*44.1*	9	*43.3*	12	*87.4*
Two or more races	0	*1.9*	0-1	*1.9*	1	*3.8*
Racial Category: Total of all participants*	4	*50.5*	11	*49.5*	15	*100*
Source: Adapted from U.S. Census Bureau, 2017. *Totals may not equal 100 due to rounding.						

4.3.2 INCLUSION OF CHILDREN

This protocol does not include children as the number of children with this type of cancer is limited.

4.4 **REGISTRATION PROCEDURES**

There is no randomization for treatment in this study. Participants will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care.

4.4.1 OHSU REGISTRATION

Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (CRMS, e.g., eCRIS). The OHSU coordinating center team will verify completeness of documents, enter registration information into the CRMS, and assign a study number/identifier. At a minimum, registration of OHSU participants will include signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization.

4.5 PARTICIPANT SCREENING AND ENROLLMENT

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

Screening will begin once the participant has provided written informed consent to participate in the study and ends on Day 1 of the study. All screening and baseline evaluations will be performed during the screening phase (i.e., up to 28 days before on-study treatment is initiated). Day 1 of the clinical trial will be when participants are administered first dose of SBRT. Total accrual of all participants is anticipated to take a total of 12 month.

4.6 PARTICIPANT WITHDRAWAL OR DISCONTINUATION

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. If a participant no longer wants to receive investigational product, but is willing to come for follow-up appointments, the participant's request should be honored, if possible. The following are examples demonstrating why a participant's treatment might be discontinued.

- Toxicity precludes further study treatment.
- There is a need for any treatment not allowed by the protocol.
- The participant fails to meet the criteria for study treatment.
- Pregnancy or intent to become pregnant.
- Disease recurrence or progression.
- Investigator's discretion.

No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation and collection of any new or ongoing adverse events (AEs) should be collected at the time the participant withdraws consent.

For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 6.8.

4.6.1 HANDLING PARTICIPANT WITHDRAWAL AND DISCONTINUATION

Participants enrolled in this study that withdraw prior to initiating on-study treatment will be replaced.

4.7 OFF-STUDY CRITERIA

Criteria that can take a participant off-study include:

- Participant requests to be withdrawn from study without further follow-up,
- Completed study follow-up period,
- Progression of disease,
- Death,
- Screen failure,
- Investigator's discretion

4.7.1 SCREEN FAILURES

Any participant that has signed the consent form (for either screening or study participation) but does not meet the study eligibility criteria, or meets study eligibility criteria but terminates their participation prior to receiving study treatment, will be considered a screen failure. The reason for screen failure should be captured in the database for each participant failing to meet the eligibility criteria.

4.8 **STUDY DISCONTINUATION**

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to IRB and other regulatory authorities (as applicable). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Reasons for terminating the study may include the following:

- Incidence or severity of adverse events, in this or other studies, indicates a potential health hazard to participants.
- Data that are not sufficiently complete and/or evaluable.
- Investigator(s) do not adhere to the study protocol, or applicable regulatory guidelines in conducting the study.
- Participant enrollment is unsatisfactory.
- Submission of knowingly false information from the study site to regulatory authorities.
- Upon instruction by local or other regulatory, or oversight authority.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor, IRB and/or other regulatory authority (e.g. FDA).

5. TREATMENT PLAN

5.1 DOSAGE AND ADMINISTRATION

On-study treatment will be administered on an out-patient basis. Reported adverse events and potential risks are described in Section 8.4. Appropriate dose modifications are described in Section 5.2, Dose modifications. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1.1 SIMULATION

All imaging for radiation planning will be performed according to institutional guidelines. If deemed necessary by the treating radiation oncologist for targeting purposes, eligible participants will undergo placement of intrahepatic fiducial markers prior to simulation (refer to Section 6.1.7). Imaging for radiation planning will include triple-phase contrast-enhanced simulation with immobilization. Participants will be immobilized with standard motion management techniques. The simulation should be performed with the participant in treatment position (i.e., supine, with arms above head).

5.1.2 TARGET AND NORMAL STRUCTURE CONTOURING

Diagnostic CT scans and MRIs (if available) will be fused to the CT simulation for contouring purposes to help guide contouring of target and normal structures, which will be recorded on the CT images. Normal structures to be contoured include spinal cord, esophagus, heart, chest wall, body, stomach, duodenum, small bowel, large bowel, lung, liver, and kidneys.

The gross tumor volume (GTV) (or internal target volume (ITV) if 4-dimensional CT is utilized) will be contoured using all available images, and the planning target volume (PTV) will be constructed using a 5 mm circumferential margin. All participants must have a critical volume of liver minus GTV (or ITV) of at least 700 cm^3.

If tumor motion is greater than 3 mm, participants will be simulated and treated with a breathhold technique. In breathhold technique, the participant is treated in a specific inspiratory phase of the respiratory cycle. If appropriate and at the discretion of the treating physician, participants may also undergo a MRI simulation in the treatment position to assist in the contouring of tumor and normal structure. If performed, MRI should be done with contrast.

5.1.3 RADIATION THERAPY

A total of 40 Gy will be administered to the PTV in 5 fractions given every other day, provided that normal organ constraints are met (i.e., uninvolved liver volume of ≥700 cc).

If normal organ constraints are not met, the dose will be iteratively de-escalated to two dose levels (35 Gy in 5 fractions, then 30 Gy in 5 fractions)(**Table 2**). If normal organ constraints are unable to be met at 30 Gy in 5 fractions, the patient is deemed ineligible for SBRT and is considered a screen failure. Cone-beam CT will be obtained prior to each fraction delivered.

Table 2. SBRT – Dose Modification	
Dose Level	**Liver-directed SBRT**
0*	40 Gy in 5 fractions
-1	35 Gy in 5 fractions
-2	30 Gy in 5 fractions
*Dose level -1 and -2 are treatment doses for patients requiring a dose reduction from the starting dose level (0).	

5.1.4 PLANNING CONSTRAINTS

Dose constraints for normal organs at risk including spinal cord, esophagus, heart, chest wall, skin, stomach, duodenum, small bowel, large bowel, lung, liver, and kidneys will be according to institutional standards for liver SBRT (**Table 3**).

Table 3. Dose Constraints			
Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)****
CORD	0.1cc <0.35 cc <1.2 cc	25 Gy 23 Gy (4.6 Gy/fx) 14.5 Gy (2.9 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus*	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	38 Gy (7.6 Gy/fx)
Chest wall/Rib	<30 cc	35 Gy (7 Gy/fx)	43 Gy (8.6 Gy/fx)
Skin	<10 cc	36.5 Gy (7.3 Gy/fx)	39.5 Gy (7.9 Gy/fx)
Stomach	0.1cc <10 cc	27.5 Gy 18 Gy (3.6 Gy/fx)	32 Gy (6.4 Gy/fx)
Duodenum*	0.1cc <5 cc <10 cc	30 Gy 18 Gy (3.6 Gy/fx) 12.5 (2.5 Gy/fx)	32 Gy (6.4 Gy/fx)
Small bowel*	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)
Large Bowel*	<20 cc	25 Gy (5 Gy/fx)	38 Gy (7.6 Gy/fx)
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	
$Lung_{Total}$	1500 cc	12.5 Gy (2.5 Gy/fx)	
$Lung_{Total}$	1000 cc	13.5 Gy (2.7 Gy/fx)	
$Liver_{GTV}$	700 cc	15 Gy (3 Gy/fx)	21 Gy (major dev)
$Kidney_{Total}$	200 cc	17.5 Gy (3.5 Gy/fx)	
*Avoid circumferential irradiation ** “point” defined as 0.035cc or less			

The PI will perform RT Quality Assurance Reviews of all plans within 10 days of patients starting the treatment.

5.2 DOSING DELAYS AND MODIFICATIONS

SBRT will be delivered in a total of 5 fractions over two weeks, with treatments delivered every other day between Monday and Friday. SBRT will not occur on Saturdays, Sundays or holidays. There should be no more than a 14 day interruption between the planned administration of each fraction. Dosing interruptions lasting longer than 14 days between each fraction, for any reason, are considered an unacceptable and participants will be removed from

study and replaced with another participant. Participants removed from study will be treated per institutional standards or offered participation in another clinical trial if one is available. All dosing interruptions should be recorded in CRF.

5.3 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and general medical guidelines for the care of participants undergoing treatment of HCC. Supportive care guidelines for radiation therapy are described in Table 4. Additional supportive care procedures and any premedications, according to institutional guidelines, include hydration, pain management, anti-emetics, and treatment interruption in case of severe radiation-related symptoms.

Table 4. Supportive care guidelines for radiation therapy

Adverse effect	**Support Treatment**
Psychological	
Depression:	Selective serotonin reuptake inhibitors effective for depression but not for fatigue
Fatigue:	Exercise; sleep hygiene, stress reduction, cognitive and relaxation therapies
Skin	
Dermatitis:	Moisturizing creams; routine skin care with mild, unscented soap
Radiation recall:	Same as dermatitis
Cardiovascular and pulmonary	
Cardiovascular disease:	Cardiovascular monitoring (ECG)
Gastrointestinal	
Diarrhea	Loperamide
Genitourinary	
Urinary obstruction	Tamsulosin (for males) administered according to institutional guidelines
Cystitis:	Pyridium (both males and females) administered according to institutional guidelines
Infertility / teratogenicity:	Egg and sperm preservation; ovarian transposition

5.3.1 CONTRACEPTION

SBRT may have adverse effects on a fetus in utero, and may have adverse effects on the composition of sperm. People may be enrolled if they are willing to use methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive people are defined as: 1) surgically sterilized or biologically absent reproductive organs, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for more than 1 year), or 3) not heterosexually active for the duration of the study. Birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Participants should start using birth control from study visit 1 throughout the study period up to 120 days after the last dose of study therapy.

5.3.2 USE IN PREGNANCY

If a participant inadvertently becomes pregnant while receiving SBRT, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The site will report the outcome of the pregnancy to Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).The pregnancy will be recorded on the CRF and reported by the Investigator to the IRB. Refer to Section 8.6.

5.4 **PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES**

Herbal supplements will be allowed on study and noted on CRF. For patients with contrast allergy, steroids will be allowed for CT scans.

Participants are prohibited from receiving the following therapies during the Screening and Treatment Period of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Chemotherapy not specified in this protocol.
- Investigational agents other than those described in this protocol.
- No radiation therapy other than what is allowed in this study.

Participants who require the use of any of the aforementioned treatments for clinical management may, at the discretion of the investigator, be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

Participant exclusion criteria (Section 4.2) describes other medications prohibited in this trial.

6. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

6.1 STUDY SPECIFIC PROCEDURES

6.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any prior conditions that are considered to be clinically significant by the PI. Details regarding the participant's cancer will be recorded separately and not listed as medical history.

6.1.2 DISEASE ASSESSMENT

The investigator or qualified designee will obtain prior and current details regarding the participant's cancer.

6.1.3 MEDICATION HISTORY

A complete medication history will be acquired concurrent with medical history. Concomitant prescription, over-the-counter medications and any supplements or herbals should be captured prior to start of SBRT.

6.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits and per institutional standards. The physical examination to be conducted will include an evaluation of: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; lymphatic system, musculoskeletal system, and nervous system. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings. All physical examinations will also include:

6.1.4.1 *Vital signs*

Vitals to be collected include BP, HR, temperature, and oxygen saturation by pulse oximetry. As part of screening/baseline visit, vitals should be obtained within 14 days prior to first dose of SBRT. Vitals will also be obtained during treatment.

Significant findings that were present prior to the signing of the informed consent must be included in the Medical History CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event CRF.

6.1.4.2 *Height and weight*

Height, weight, body surface, will be collected at initial radiation oncology consultation.

6.1.4.3 *Performance status*

Performance status will be determined for all participants at screening and at select times during treatment as per assessment schedule in Section 6.8. Refer to Appendix B for performance criteria.

6.1.5 RADIOGRAPHIC OR OTHER IMAGING ASSESSMENTS

All imaging for radiation planning and subsequent follow-up will be in accordance with institutional standards, and include (but are not limited to): multiphasic CT (4D-CT), CT, MRI, X-ray, Fluorodeoxyglucose (FDG) Positron emission tomography (PET), and ultrasound. Cone-beam CT will be obtained prior to each fraction delivered. Imaging procedures will occur according to Section 6.8, Schedule of Events, but may occur more frequently if clinically indicated.

6.1.6 ADVERSE EVENT EVALUATION

Toxicities and adverse experiences will be assessed at each visit using the CTCAE v5.0 and quantifying current Child-Pugh score to assess risk of RILD. Adverse events will be monitored from the time the participant signs the Consent Form up until 3 months following SBRT. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs up until 3 months following radiation therapy. All AEs (serious and non-serious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with the study therapy.

For details on AE collection and reporting, refer to Section 8.6.

6.1.6.1 *Radiation-induced liver toxicity*

Radiation-induced liver disease (RILD) is defined as either classical or non-classical RILD. Classical RILD (typically occurring in patients without background liver dysfunction or cirrhosis) is characterized as the presence of nonmalignant ascites and anicteric elevation of alkaline phosphatase level twice the upper level of normal or baseline value occurring between 2 weeks and 3 months after the completion of irradiation. Non-classical RILD (typically occurring in patients with baseline liver dysfunction or cirrhosis), occurs is defined as grade 4 AST and/or ALT elevations, or an increase in CP score of ≥ 2 within 1 week to 3 months after completing SBRT.[26]

6.1.7 FIDUCIAL MARKER PLACEMENT

The type of fiducial along with method implantation will be according to institutional standards and at the discretion of the treating radiation oncologist, as some tumors may be targetable without fiducial guidance. Participants should discontinue antiplatelet medications approximately 7 days before the fiducial implantation. In general, warfarin should be discontinued 5 days before insertion, and heparin and related products discontinued approximately 12-24 hours prior to the procedure. Absent any complications, these treatments may be approximately restarted 24-48 hours following the procedure.

6.1.8 ASSESSMENT OF PARTICIPANT-REPORTED OUTCOMES

Quality of life (QoL) care metrics using the will be assessed using the EORTC QLQ-C30 and FACT-Hep questionnaires at time points shown in Section 6.8, Schedule of Events. The questionnaire will each take <45 minutes to complete.

6.2 **LABORATORY PROCEDURES AND EVALUATIONS**

6.2.1 HEMATOLOGY

Hematologic profiling will be collected per institutional standards, and should include evaluation of hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.

6.2.2 BIOCHEMISTRY

Blood chemistry will be collected per institutional standards and should include the following: Liver function test (LFT), including: Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, AST, ALT serum creatinine, blood urea nitrogen, calcium, potassium, and alpha-fetoprotein tumor marker (AFP).

6.2.3 COAGULATION PANEL

INR will be collected for calculation of CP score

6.2.4 ECHOCARDIOGRAM

As clinically indicated.

6.2.5 PREGNANCY TEST

A serum or urine pregnancy test is required during screening for all persons of childbearing potential. The pregnancy test is required within 72 hours prior to study intervention and results must be available prior to administration of SBRT. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

6.3 **SCREENING ASSESSMENTS**

A screening (consultation) visit may occur as part of standard of care. If a participant is eligible for the study after review of key inclusion/exclusion criteria, additional screening visits will be scheduled while staff members are requesting insurance authorization to participate in a clinical trial.

The following will be reviewed at screening visit:

- Clinical history and physical exam (per standard of care)
- Informed consent obtained and documented

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

6.3.1 SCREEN FAILURES

A participant who signed an informed consent form but does not initiate planned SBRT, for any reason, will be considered a screen failure. Those found not to be eligible after signing the study consent will be considered screening failures, and data will be handled in the same manner. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failures. No other data except reason for screen failure will be entered into the clinical database for individuals who are screen failures.

6.4 ASSESSMENTS DURING TREATMENT

Participants will be assessed once during the course of 5 fraction SBRT. Specific on-study assessments are listed in the Section 6.8, Schedule of Events. Under certain circumstances (e.g., clinic holiday, inclement weather) scheduled visits may be delayed by no more than 7 days between each visit.

6.5 FOLLOW-UP

Participants will be followed and disease assessments will take place 6 weeks following completion of SBRT, then every 3 months up until enrollment on hospice or death, or 2 years from time of last SBRT dose, whichever occurs first. Follow-up visits will be consistent with standard of care, and assessments are listed in Section 6.8. Any participants removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE.

6.6 EARLY TERMINATION OR END OF TREATMENT VISIT

Any participant that discontinues treatment earlier than planned must be evaluated within 30 days after termination or prior to the initiation of any other off-study interventional therapy, if not performed within the last 30 days. On-treatment Day 9 study visit and associated assessments (i.e., radiographic imaging and AE assessments) will serve as the end of treatment visit (Section 6.8, Schedule of Events). These assessments also pertain to participants that discontinue study intervention.

6.7 UNSCHEDULED VISITS

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (e.g., laboratory or clinical assessments) at those visits should be recorded in the CRF.

6.8 SCHEDULE OF EVENTS

Visit Days	Screening	Treatment					Follow-Up[B] (±4 weeks)
	Days	Days[†] (+7 days)					
	-28 to -1	1	3	5	7	9*	
SBRT[A]		X	X	X	X	X	
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						X[B]
Prior/concomitant medications	X						X[B]
Physical Examination[C]	X						X[B]
Radiographic Imaging	X	X[D]	X[D]	X[D]	X[D]	X[D]	X[E]
Hematology[F]	X						X[B]
Biochemistry[G]	X						X[B]
Coagulation	X						X
Pregnancy test	X						
Fiducial placement (if needed)	X						
AE assessment	X	X					X
EORTC QLQ-30	X						X[B]
FACT-Hep	X						X[B]

[†] Starting on day 1, SBRT dose fractions are given every other day (i.e., Monday-Friday), but not administered on Saturdays, Sundays, or holidays. Dosing interruptions because of weekends and holidays will be recorded in CRF.

[*]Day 9 study assessments of radiographic imaging and AE collection will serve as Early Termination and/or End of Treatment Visit.

[A] Scheduled SBRT visits may be delayed by no more than 7 days between each visit, or may occur earlier than scheduled by no more than 3 days.

[B] Follow-up assessment to occur 6 weeks following completion of SBRT then every 3 months up to 2 years post SBRT therapy

[C] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be measured at screening visit only.

[D]Cone-beam CT will be obtained prior to each SBRT fraction.

[E] Participants will undergo surveillance imaging (e.g., CT scan) 6 weeks following completion of SBRT and then every 3 months for the first 2 years.

[F] Hemoglobin, platelets and white cell count with differential white count

[G] Biochemistry to include renal (creatinine, urea, sodium, potassium) and liver function (AST, ALT, bilirubin)

[H]AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0 as well as definition of radiation-induced liver disease (Child-Pugh elevation of 2 or more). All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record all AEs and SAEs occurring from the time of consent signing to 3 months following the completion of SBRT.

7. EFFICACY MEASURES

Where applicable, tumor response will be determined per the investigators' assessment, according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).[27,28]

7.1 DEFINITION OF EFFICACY MEASURES

Evaluable for response. The analysis population to assess efficacy endpoints (e.g., local control rate, intrahepatic disease free survival, and overall survival), will include only participants who have received at least 85% of the prescribed SBRT dose (i.e., 85% Level 0 = 34 Gy; 85% Level -1 = 30 Gy; 85% Level -2 = 25.5 Gy). Participants that experience more than 14 days of dose interruption, after having received ≥ 85% of the prescribed SBRT dose will be included for analysis.

7.1.1 DISEASE PARAMETERS

Measurable disease. The lesion is considered as a RECIST measurable so long as the lesion can be accurately measured in at least one dimension as 1 cm or more.

HCC Target lesions. Measured in two perpendicular axes = longest diameter (long axis) and their longest perpendicular (short axis). The sum of the products of the diameters is defined (Σ long-axis diameter × short-axis diameter in mm^2). Up to 6 lesions/patient, representing the largest possible number of anatomical sites, with a preference for the largest lesions and mediastinal and retroperitoneal sites.

Consider the following for cases in which lesions show partial internal necrosis:

- The measurement of the viable tumor should be performed on CT or MRI obtained in the arterial phase, when the contrast between viable vascularized tumor tissue and non-enhancing necrotic tissue is the highest.
- The longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured: a thorough careful evaluation of the CT or MRI scans is required.
- The measurement of the viable tumor diameter should not include any major intervening areas of necrosis.

HCC Non-target lesions. Measurable lesions not selected as targets and non-measurable lesions. Lesion too small (< 10 mm), infiltrating or atypical enhancement (non-arterial).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node longest diameter must be > 15 mm or short axis >10 mm.

7.2 DISEASE EVALUATION

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: Participants should be followed with either contrast-enhanced spiral computed tomography (CT) – preferably with use of multi-slice scanners – or contrast enhanced dynamic magnetic resonance imaging (MRI). The administration of intravenous contrast is recommended for all CT or MRI studies if not medically contraindicated. For multidetector CT scanners that are capable of acquiring very thin slices, it is necessary to keep in mind that it is mandatory to use contiguous slices for image read and interpretation, to avoid missing small lesions. The analysis of contiguous slices with traditional 5 mm thickness and 5 mm reconstruction interval is acceptable; however, the analysis of 2.5 mm thickness slices at 5 mm intervals is not acceptable.

7.3 **EFFICACY CRITERIA FOR TUMOR RESPONSE**

7.3.1 EVALUATION OF TARGET LESION

Progressive Disease (PD):	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-Progressive Disease	Any cases that do not qualify for progressive disease

7.3.2 EVALUATION OF NON-TARGET LESION

Non-Progressive Disease	Any cases that do not qualify for progressive disease
Progressive Disease (PD):	Appearance of one or more new lesions. See 7.3.2.1

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the principal investigator.

7.3.2.1 *Evaluation of New Lesions*

A new liver nodule is classified as HCC, and will therefore be declared as a progression, when its longest diameter is ≥ 10 mm and it presents the typical enhancement of HCC on dynamic imaging, i.e. contrast uptake during the arterial phase with portal vein/delayed phase washout. Liver lesions ≥ 10 mm, which do not exhibit typical enhancement dynamics may be diagnosed as HCC if they increase of ≥ 10 mm on subsequent scans. In this latter case, the date of progression used a posteriori will be the date of first detection of the lesion.

7.3.3 LOCAL CONTROL RATE

Local control is defined as the absence of progressive disease (per Section 7.3.1) within the PTV or at the PTV margin, measured from time of first SBRT dose to time of progression or transplantation, or 2 years from last SBRT dose, whichever occurs first.

7.3.4 INTRAHEPATIC PROGRESSION-FREE SURVIVAL

Intrahepatic progression-free survival (PFS) is defined as the development of intrahepatic recurrent or new disease within any section of the liver, including the PTV. The consideration of whether a lesion is within or adjacent to the PTV is determined by the individual site investigator. Intrahepatic PFS is measured from time of first SBRT dose to time of progression or transplantation, or 2 years from last SBRT dose, whichever occurs first.

7.3.5 OVERALL SURVIVAL

OS is defined as the time after having completed at least 85% of the prescribed SBRT dose up time of death, or 2 years from last SBRT dose, whichever occurs first.

7.4 **RESPONSE REVIEW**

Response assessment will be determined by the investigator.

7.5 **MILAN CRITERIA**

Participant eligibility for transplantation will be based on guidelines reported by Mazzaferro et al.[6] To be considered eligible for liver transplantation, participants with HCC must have disease as follows:

- Single tumor with diameter ≤5 cm OR up to 3 tumors, each with diameter ≤3 cm, AND
- No major vessel or extra-hepatic involvement.

8. SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 6.8, Schedule of Events. Any clinically significant adverse events persisting at the end of treatment visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

8.2 DEFINITIONS

8.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

8.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or

- The development of drug dependency or drug abuse.

8.2.3 UNANTICIPATED PROBLEMS (UP)

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

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

This study will use the OHRP definition of UP.

8.2.4 SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

- **Mild** (grade 1) – An event that is usually transient in nature and generally not interfering with normal activities
- **Moderate** (grade 2) – An event that is sufficiently discomforting to interfere with normal activities
- **Severe** (grade 3) – An event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity
- **Life-threatening/debilitating** (grade 4) – An event that puts the participant at immediate or potential risk of death, requires hospitalization, or which drastically impacts a participant's well-being
- **Fatal** (grade 5)

8.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- *Definite* – The AE is clearly related to the study treatment.
- *Probable* – The AE is likely related to the study treatment.
- *Possible* – The AE may be related to the study treatment.
- *Unlikely* – The AE is doubtfully related to the study treatment.
- *Unrelated* –The AE is clearly NOT related to the study treatment.

8.3 **EXPECTEDNESS**

The investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.4 ADVERSE EVENT LIST(S)

8.4.1 ADVERSE EVENT LIST FOR SBRT

Rates of non-classical RILD (defined as a CP elevation of 2 or more within 3 months after radiation) are reported to be in the range of 20-30%.

Rates of Grade CTCAE 1-2 toxicities are reported to range from 0-27% and Grade 3-4 toxicities are observed in around 5%. The most commonly reported toxicities are fatigue, right upper quadrant pain, low-grade pyrexia, and elevation in transaminase. Minor pain, fever and chills (Grade 1) is observed in 14% of patients. Gastric ulceration and esophagitis occurred at rates of 7% (Grade 2) and 3% (Grade 3), respectively.

8.5 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

AEs will be evaluated using the current version of the CTCAE v5.0 from the time the participant signs the consent form to 3 months following SBRT.

8.6 REPORTING PROCEDURES

8.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

8.6.2 MEDWATCH REPORTING

The Investigator is required to report AEs to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the investigational product.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500, the MedWatch Voluntary Reporting form (available here), or completed online. A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder.

8.6.3 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy should be recorded on the CRF and reported by the Investigator to the IRB. Pregnancy follow-up should be reported using the same form. Any SAE experienced during pregnancy must be reported.

If while on study treatment a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

8.7 **STUDY STOPPING RULES**

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected
- Death suspected to be related to SBRT

9. STATISTICAL CONSIDERATIONS

Refer to Section 3.1, Description of the Study Design for a detailed description of the study design and endpoints.

9.1 ANALYSIS POPULATIONS

Safety analysis set: All participants will be evaluable for toxicity from the time of their first fraction of SBRT.

Efficacy analysis set: The analysis population to assess transplantation eligibility (i.e., Milan criteria) and efficacy endpoints (e.g., localized control rate, intrahepatic progression, extrahepatic progression and overall survival), will include only participants who have received at least 85% of the prescribed SBRT dose (i.e., 85% Level 0 = 34 Gy; 85% Level -1 = 30 Gy; 85% Level -2 = 25.5 Gy).

9.2 DESCRIPTION OF STATISTICAL METHODS

9.2.1 GENERAL APPROACH

This is a pilot study to assess the feasibility of bridge-to-transplantation using SBRT for patients with severe liver disease.

9.2.2 ANALYSIS OF PRIMARY ENDPOINT

Using the efficacy analysis set, the proportion of transplant eligible participants at 1 year (per Milan criteria, Section 7.5) will be measured from time of first SBRT dose, reported with 95% exact confidence interval (CI).

9.2.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Using the efficacy analysis set, the estimate of local control rate, intrahepatic progression free survival, and overall survival, will be plotted using Kaplan-Meier curve and reported with median survival and 95% CI if available. Using the same efficacy analysis set, the proportion of participants that proceed to transplantation, will be measured and reported with 95% CI.

Non-classic RILD, liver toxicity defined as a ≥ 2 increase in CP score (**Appendix A**), and liver toxicity per CTCAE v5.0, will be estimated along with an exact CI using the safety analysis set.

9.2.4 ANALYSIS OF THE EXPLORATORY ENDPOINT

The QoL scores will be recorded over time (See Sections 6.1.8 and 6.8) using the EORTC QLQ-C30 and FACT-Hep questionnaires. Summary of QoLs and its change over time will be presented graphically using box plot and spaghetti plot, in addition to a summary table of QoL over time. No hypothesis testing is planned for QoL.

Descriptive statistical analysis, utilizing the efficacy analysis set, will be used to measure the proportion of histopathologic changes in irradiated tumor sites relative to uninvolved liver tissue will be measured.

9.3 SAMPLE SIZE, POWER, ACCRUAL RATE AND STUDY DURATION

9.3.1 SAMPLE SIZE AND POWER

The primary goal of this pilot study is to help identify unforeseen problems with a subsequent larger-scale clinical trial. We predict that there is a 20% probability that a particular patient's treatment plan will fail to meet all dosimetric constraints[29], most notably the 700 cc critical volume constraint for the liver minus GTV since many cirrhotic patients have small total liver volumes, rendering them ineligible for SBRT. A sample size of 15 patients will ensure that we will encounter at least one incidence of SBRT ineligibility at a 95% CI.[30]

9.4 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

10. CLINICAL MONITORING

10.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

This study is under the oversight of the Knight Cancer Institute's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

The Knight DSMC will review and monitor study progress, toxicity, safety and other data from this study. Information that raises any questions about participant safety or protocol performance will be addressed by the Investigator, statistician and study team. Should any major concerns arise, the Knight DSMC may recommend corrective action and determine whether or not to suspend the study.

The Knight DSMC will review each protocol every 6 months, but may occur more often, if required, to review toxicity and accrual data (please refer to Knight DSMP for additional details on audit frequency). The Knight DSMC will review accrual, toxicity, response and reporting information. Information to be provided to the DSMC may include: participant accrual; treatment regimen information; AEs and SAEs reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

10.2 CLINICAL DATA & SAFETY MONITORING

The OHSU Investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all participating sites, and final analysis of study data.

In the absence of a formal monitoring plan, the Investigator may work with his/her study team to conduct and document internal monitoring of the study to verify protection of human participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If at any time Investigator noncompliance is discovered at OHSU, the Investigator shall promptly either secure compliance.

Independent audits will be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

10.3 QUALITY ASSURANCE & QUALITY CONTROL

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

Quality assurance (QA) auditing activities will occur as detailed in the Knight DSMP. All discrepancies, queries, deviations, observations, and findings will be compiled into a final audit report along with a Corrective and Preventative Action Plan.

The Sponsor-investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

11. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

11.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate CRFs, and source documentation.

11.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

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

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

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, all study databases will be de-identified and archived within the Knight Cancer Institute.

11.3 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC), REDCap, system on OHSU secure servers, which facilitates information being stored in a unified format and location. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Data from correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 10.3, Quality Assurance & Quality Control.

11.4 **MAINTENANCE OF RECORDS**

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

11.5 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

12. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

12.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 INSTITUTIONAL REVIEW BOARD

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

12.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

12.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

12.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB (and other regulatory bodies, as applicable) within 5 business days after the implementation.

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APPENDIX A: CHILD-TURCOTTE PUGH SCORE

The Child-Turcotte-Pugh (CP) scoring system utilizes the serum bilirubin, serum albumin, prothromin time (PT)/ international normalized ratio (INR), degree of ascites and degree of hepatic encephalopathy and assigns 1–3 points for each variable. Patients are divided into three classes based on total points with ≤6, 7–9, and ≥10 points representing Child's class A, B, and C, respectively.

Child-Pugh-Turcotte Score

	Variable score 1	Variable score 2	Variable score 3
Serum albumin (g/dL)	>3·5	2·8–3·5	<2·8
Ascites	Absent	Mild to moderate (diuretic controlled)	Severe (diuretic refractory)
Prothrombin time (INR)	<1·7	1·7–2·3	>2·3
Encephalopathy	Absent	Mild to moderate (grade 1–2)	Severe (grade 3–4)
Total bilirubin (mg/dL)	<2	2–3	>3

Interpretation -Points	Class
5-6	A
7-9	B
10-15	C

APPENDIX B: PERFORMANCE STATUS

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

APPENDIX C: CONTRACEPTION

Females of childbearing potential who are sexually active with a non-sterilized male partner or partners of male participantmust use 2 highly effective method of contraception. These include: levonorgestrel-releasing intrauterine system (e.g., Mirena®), copper intrauterine device, and hormonal methods. Appropriate hormonal contraceptives include: Etonogestrel-releasing implants (e.g. Implanon® or Norplant®), ethinylestradiol/etonogestrel-releasing intravaginal devices (e.g. NuvaRing®), medroxyprogesterone injection (e.g., Depo-Provera®), normal and low dose combined oral contraceptive pill, norelgestromin/ethinylestradiol-releasing transdermal system (e.g. Ortho Evra®), progesterone based oral contraceptive pill using desogestrel (NB, Cerazette® is currently the only highly effective progesterone-based)

Non-sterilized male participants, or partners of female participant, must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Abstaining from sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice for both female and male participants; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female participant should also refrain from breastfeeding throughout this period.