NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 1112

(ClinicalTrials.gov NCT #: 01730937)

Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma

Amendment 12: September 23, 2022

NRG Oncology

RTOG 1112

RANDOMIZED PHASE III STUDY OF SORAFENIB VERSUS STEREOTACTIC BODY RADIATION THERAPY FOLLOWED BY SORAFENIB IN HEPATOCELLULAR CARCINOMA

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

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Protocol Agent

Agent	Supply	NSC #	IND #
Sorafenib	Commercial	724772	Exempt

Participating Sites (5/7/13)
☐ US Only
☐ Canada Only
☒ US and Canada
☒ Approved International Member Sites

Document History

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NRG Oncology (27Oct2017)

The following NCTN Study Champion(s) have been added to this trial:
ALLIANCE: Theodore S. Hong, MD
SWOG: Tim Mitin, MD, PhD

<table>
<tr><td colspan="3">CONTACT INFORMATION (23-SEP-2022)</td></tr>
<tr><td>For regulatory requirements:</td><td>For patient enrollments:</td><td>For study data submission:</td></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
(Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission.)

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

Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923 or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website located (https://www.ctsu.org). Access to the CTSU members' web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u>: Contact the study data manager listed on the NRG Oncology contact information table on the protocol cover page.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">For imaging data submission questions:
IROCimagearchive@acr.org; please include trial number in the email subject line

For TRIAD access and installation support:
TRIAD-Support@acr.org
Triadhelp.acr.org

TRIAD Software Installation:
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RADIATION THERAPY ONCOLOGY GROUP

RTOG 1112

Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy followed by Sorafenib in Hepatocellular Carcinoma

SCHEMA (25-MAR-2020)

	STRATIFY	Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none) Hepatitis B or B and C vs. C vs. other North American site vs. Non-North American site HCC volume/liver volume (<10% vs. 10-40 vs. >40%)	**RANDOMIZE**	**Arm 1** Daily sorafenib
				Arm 2 SBRT alone (27.5 Gy – 50 Gy in 5 fractions) Followed by Sorafenib alone daily

See Section 5.0 for radiation therapy credentialing details. See Section 7.0 for details/doses of sorafenib.

Protocol treatment is encouraged to begin as soon as possible after study entry. Protocol treatment must begin within 21 days after study entry, unless extra time is needed for fiducial marker insertion, but not to exceed 28 days.

Patient Population: (See Section 3.0 for Eligibility)
Unsuitable for resection or transplant or radiofrequency ablation (RFA)
Unsuitable for TACE or refractory to TACE
Barcelona Clinic Liver Cancer Stage (BCLC) Intermediate (B) or Advanced (C)

Required Sample Size: 292

ELIGIBILITY CHECKLIST **(13-MAY-2019)**

NRG Oncology Institution #
RTOG 1112
Case #

Patients must have a diagnosis of HCC by at least one criterion listed below in Q1-3:

1 _____(Y/N) Does the patient have pathologically (histologically or cytologically) proven diagnosis of HCC within ≤360 days prior to study entry? (The HCC must be >1cm).

2_____(Y/N) Does the patient have at least one solid liver lesion >1cm with arterial enhancement and delayed washout on multi-phasic computerized tomography (CT) or magnetic resonance imaging (MRI) in the setting of cirrhosis or chronic hepatitis B or C without cirrhosis within ≤360 days prior to study entry?

3_____(Y/N) Does the patient have enhancing vascular thrombosis (involving portal vein, IVC and/or hepatic vein) demonstrating early arterial enhancement and delayed washout on multi-phasic CT or MRI, within ≤360 days prior to study entry in a patient with known HCC (diagnosed previously ≤720 days prior to study entry), using criteria in 3.1.1a or 3.1.1b of the protocol?

4 _____(Y) Does the patient have measureable hepatic disease and/or presence of vascular tumor thrombosis (involving portal vein, IVC and/or hepatic vein) which may not be measureable as per RECIST, as defined in Section 11.0) on liver CT or MRI within 28 days prior to study entry?

5 _____(Y) Has the patient had a history/physical examination, including examination for encephalopathy, ascites, weight, height, and blood pressure within 14 days prior to study entry?

6 _____(Y) Was an assessment by radiation oncologist and medical oncologist or hepatologist who specializes in treatment of HCC performed within 28 days prior to study entry?

7 _____(Y/N) Did the patient have a Multiphasic liver CT or multiphasic liver MR scan-. And CT chest with CT or MR abdomen and CT or MR pelvis, or PET CT chest/abdomen/pelvis within 28 days prior to study entry?

8 _____(Y) Was the Zubrod Performance Status 0-2 within 28 days prior to study entry?

9 _____(Y) Did all blood work meet the requirements, per Section 3.1.6 of the protocol?

10 _____(Y) Is the BCLC stage: Intermediate (B) or advanced (C) within 28 days prior to study entry?

11 _____(Y) Is the Child-Pugh score A within 14 days prior to study entry?

12 _____(Y) Age ≥ 18?

13 _____(Y/N) Is the patient a woman of childbearing potential?
Y If yes, does she agree to practice adequate contraception while on study and for at least 6 months following the last dose of radiation therapy and for at least 28 days following the last dose of sorafenib (whichever is later)?

14 _____(Y/N) Is the patient a male?
Y If yes, does he agree to practice adequate contraception while on study and for at least 6 months following the last dose of radiation therapy and for at least 28 days following the last dose of sorafenib (whichever is later)?

15 _____(Y) Is the patient unsuitable for resection or transplant or radiofrequency ablation (RFA)?

16 _____(Y) Unsuitable for or refractory to transarterial hepatic chemo-embolization (TACE) or drug eluting beads (DEB) per Section 3.1.11 of the protocol?

17 _____(Y/N) Has the patient received prior TACE or DEB?
Y If yes, was it > 28 days prior to study entry?

18 _____(Y) Did the patient provide study-specific informed consent prior to study entry?

19 _____(Y/N) Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer)?
Y If yes has the patient been disease free for a minimum of 2 years?

20 _____(N) Prior sorafenib use > 60 days?

21 _____(N) Prior radiotherapy to the region of the liver that would result in excessive doses to normal tissues due to overlap of radiation therapy fields?

22 _____(N) Prior selective internal radiotherapy/hepatic arterial Yttrium therapy?

23 _____(N) Does the patient have any of the severe, active co-morbidity, as defined in Section 3.2.5 of the protocol?

24 _____(N) Does the patient have any one hepatocellular carcinoma > 15 cm in maximal diameter?

25 _____(N) Is the total sum of maximal diameters of each definite parenchymal hepatocellular carcinomas or the maximal diameter of a single conglomerate HCC > 20 cm?

26 _____(N) Are there more than 5 discrete intrahepatic parenchymal foci of HCC?

27 _____(N) Is there direct tumor extension into the stomach, duodenum, small bowel or large bowel?

28 _____(N) Is there measureable common or main branch biliary duct involvement with HCC?

29 _____(N) Are there extrahepatic metastases or malignant nodes (that enhance with typical features of HCC) > 3.0 cm, in sum of maximal diameters (e.g. presence of one 3.4 cm metastatic lymph node or two 2 cm lung lesions)?

30. _____ (Y/NA) Is the patient HIV positive with CD4 count ≥ 350 cells/microliter and on highly active antiretroviral therapy?

31 _____(N) Has the patient had a prior liver transplant?

The following questions will be asked at Study Registration:
IMRT, SBRT, and IGRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.
PROTON CREDENTIALING IS REQUIRED IF USING PROTONS.

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient Initials (Last First Middle)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date

_____ 18. Medical oncologist's name

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____ (N/Y) 24. Did the patient agree to participate in the quality of life component?

_____ If no, please specify the reason from the following:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____ 25. Vascular involvement
(1) IVC/main portal vein/ right or left main branch portal vein or
(2) other vascular involvement or
(3) none

_____ 28. Hepatitis Status
(1) B
(2) C
(3) other

_____ 29. Site
(1) North American
(2) Non-North American

_____ 30. HCC volume/(liver volume including HCC volumes)
(1) <10%
(2) 10-40%
(3) >40%

_____ 31. Specify treatment technique/machine:
(1) 3D-CRT
(2) IMRT
(3) Cyberknife
(4) Protons

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the fifth most common solid organ cancer and the third most common cause of cancer death globally, responsible for an estimated 600,000 deaths annually (Jemal 2010). Although HCC is less common in North America, the incidence has increased from 1.4 to 2.4 per 100,000 over the past two decades, and it is expected to continue to rise in parallel to the increasing incidence of Hepatitis C.

Cirrhosis, due to alcohol, viral hepatitis, autoimmune hepatitis, hemochromatosis, or non-alcoholic steatohepatitis (NASH) increases the risk of HCC developing. Patients with Hepatitis C cirrhosis have a 5-20% 5-year cumulative incidence of HCC, and even in the absence of cirrhosis, hepatitis B infection is associated with a 15% risk of HCC. Many patients with cirrhosis have impaired liver function, and the degree of impairment impacts HCC prognosis and treatment options. The most commonly used measure of liver function is the Child-Pugh classification, based on the presence or absence of ascites and encephalopathy as well as bilirubin, albumin, and INR levels (Appendix VII), with worse survival in Child Pugh class C and best in Child-Pugh class A, even in the absence of HCC. The Model for End-Stage Liver Disease, or MELD (Appendix VIII), is a scoring system for assessing the severity of chronic liver disease and is useful in determining prognosis and prioritizing patients for receipt of a liver transplant. More recently it has been suggested to be useful in predicting survival in HCC patients (Huo 2007). The Barcelona Clinic Liver Cancer (BCLC) staging and treatment allocation system (Appendix V) is commonly used to describe HCC patients (Llovet JNCI 2008). This system includes Child Pugh class in addition to tumor factors.

Including operable patients, the overall 5 year survival of HCC patients is less than 10%, emphasizing the need for improved therapies.

1.2 Local-Regional Treatments for HCC

Although cure is possible following surgery or liver transplant respectively for early stage HCC, most patients are not suitable for these therapies either due to medical contraindications, excessive burden of hepatic HCC, insufficient liver functional reserve. The most widely accepted selection criteria for liver transplantation are the Milan criteria defined as a single tumor 5 cm or less or up to 3 tumors 3 cm or less, with no extrahepatic spread or macrovascular involvement. When such criteria are followed, transplantation is associated with a 5-year overall survival of approximately 70%, and the recurrence rate is less than 15%. Unfortunately, there is a substantial wait time for transplantation due to a limited availability of donors, so many patients drop off the wait list due to progression of HCC beyond the Milan criteria. For patients with a solitary HCC without vascular invasion, with Child Pugh A liver function, and no portal hypertension, partial liver resection is a treatment option. Five year survival rates are approximately 50%. Mortality in patients unsuitable for transplant or resection results predominantly from hepatic tumor progression.

Local treatments for unresectable HCCs without portal vein thrombosis, include radiofrequency ablation (RFA) or other ablative approaches, which are associated with excellent local control (80-90%) for tumors away from large vessels and less than 3 cm, with reduced local control for larger tumors.

For patients with large or multifocal tumors, regional therapies may be a treatment option. Hepatic tumors derive 80% of their blood supply from the hepatic artery, while the adjacent liver parenchyma is supplied by the portal vein, making hepatic arterial directed therapies, such as transarterial chemoembolization (TACE), drug eluding beads (DEB) or radioembolization, relatively tumor specific. TACE has been shown in randomized trials to improve survival compared with symptomatic therapy alone, in patients without macrovascular involvement (Lo 2002, Llovet 2002). A recent review of TACE evidence concluded that absolute contraindications for TACE include severely reduced portal vein flow (e.g. from portal vein tumor or non-tumor occlusion) and untreatable arterial venous fistula. Relative contraindications included tumor size >

10 cm. Patients with main portal vein thrombosis are not recommended to be treated with TACE (Raoul 2011). There is more controversy in patients with segmental portal vein invasion. The patients not suitable for TACE and/or with recurrent or refractory disease following TACE are the target HCC population for this study.

1.3 Sorafenib

Sorafenib, a small molecule, tyrosine kinase inhibitor (TKI) with potent activity against the c-raf, VEGFfr2/3 and PDGF-alpha kinases (pathways involved in tumor proliferation and angiogenesis) is the standard therapy for locally advanced or metastatic HCC. In patients with advanced BCLC stage HCC, two randomized controlled trials [Sorafenib HCC Assessment Randomized Protocol (SHARP) (Llovet NEJM 2008) and the Asian Pacific Trial (Cheng 2009)], demonstrated a significant improved survival of patients treated with sorafenib compared to placebo. The SHARP trial of 602 HCC patients found an improvement in median survival from 7.9 to 10.7 months (p=0.00058, hazard ratio (HR) 0.69, confidence interval 0.55-0.88) and median time to progression from 2.8 to 5.5 months compared to placebo, with no significant difference in serious adverse events between the two treatment arms. In patients with major vascular involvement or extrahepatic disease, the median survival was improved from 6.7 to 8.9 months. In the Asian-Pacific trial, overall median survival was improved from 4.2 to 6.5 months (HR 0.68). Sorafenib has shown to be cost effective in the treatment of unresectable HCC using a Markov model of pooled phase III data (Carr 2010). Life-years gained were increased for sorafenib compared to best supportive care (mean ± standard deviation: 1.58 ± 0.17 vs. 1.05 ± 0.10 life-years gained/sorafenib patient and best supportive care, respectively). The majority of patients treated with Sorafenib eventually progress within the liver and die of liver failure, providing rationale to use local therapies in combination with Sorafenib.

1.4 Radiation Therapy (27Oct2017)

Historically, external beam radiation therapy (RT) has not been used to treat HCC, primarily because beyond whole liver doses of 28Gy in 2Gy fractions, the risk of radiation induced liver disease (RILD) increases. Classic RILD is a syndrome occurring most often within 2 months following radiation therapy, consisting of anicteric hepatomegaly and elevation of liver enzymes (ALP>AST). Treatment for RILD is limited and it may progress to liver failure, despite maximal supportive care. The risk of RILD in patients with Child Pugh A HCC treated with a mean dose to the whole liver of 28 Gy in 2 Gy per fraction is 5%, and the risk following 36 Gy in 2Gy per fraction is 50%. These threshold doses are reduced when the number of fractions is decreased (Pan 2010). Classic RILD is uncommon in modern radiation therapy series, when the dose to the liver can be kept below recommended levels. Non-classic RILD, referring to any decline in liver function or liver toxicity, excluding classic RILD (e.g. elevated transaminases or reduction of Child Pugh score) is more common in HCC patients treated with RT. It is more likely in patients with a higher Child Pugh score at baseline and in those with more advanced tumors requiring a larger volume of liver to be irradiated.

Technological advances in radiation treatment planning, breathing motion management and image guided radiation therapy (IGRT), have made it possible for ablative doses of radiation to be delivered safely to focal unresectable HCC, using conformal RT, SBRT or protons. Delivered doses have ranged from 60 to 90 Gy in 1.5 Gy fractions (Ben-Josef 2005) and 24 to 54 Gy in 6 fractions (Tse 2008). Objective response rates are 80-90% in HCCs less than 5 cm in maximal diameter, and in larger cancers (up to 15 cm), one year local control rates, defined as lack of progression of the irradiated lesions, range from 50% to 70%. Improved local control and survival have been seen in patients treated with higher doses. The median survival of patients with locally advanced HCC treated with a variety of fractionation ranges from 6 to 18 months (Mornex 2006, Seong 2009, Liang 2005, Liu 2004, Seong 2003, Zeng 2004, Li 2003, Guo 2003, Cheng 2000, Shim 2005, McIntosh 2009, Kim 2006). The best reported outcomes are reported from Asia following particle therapy (Chiba 2005, Bush 2004, Kawashima 2005, Kato 2004, Tsujii 2004, Mizumoto 2008, Hata 2006, Sugarhara 2010). In one prospective study, patients with Child-Pugh A liver disease and potentially resectable single HCCs, had a 5 year survival of 56% following proton therapy (Fukumitsu 2009). Given these results, the theoretical physical advantages of

proton therapy for HCC, and that few North American prospective proton studies have been conducted, there is a strong motivation to include protons in phase III studies of HCC RT. Proton and photon therapy have also been used to treat HCC with portal vein or inferior vena cava thrombosis (Huang 2009, Toya 2007, Koo 2010, Hata 2005, Yoon 2012).

Stereotactic body radiation therapy (SBRT), sometimes referred to as SABR, is a promising treatment for HCC, associated with sustained responses in the majority of treated patients. SBRT for the treatment of unresectable HCC was first reported in 1995 (Blomgren 1995), and there is a growing SBRT experience, mostly in patients with small (< 6 cm) HCC (Mendez-Romero 2006, Cardenes 2010, Kwon 2010, Seo 2010, Louis 2010), with a high local control at 1 to 2 years (70-90%). In one study of 38 HCC patients previously treated with TACE, 33 – 57 Gy was delivered in 3 fractions, with a 61% 2 year survival (Seo 2010). Doses > 42 Gy in 3 fractions were associated with improved local control. In another study of 48 patients with HCC treated with 3-fraction SBRT (30 – 39 Gy), 11 % of patients had a decline in Child-Pugh class, which was more likely if <800 cc of liver could be spared from 18 Gy or more (Son 2010).

Normal tissue complication probability (NTCP) models have been used to describe the partial liver volume tolerance to radiation, and to prospectively assign dose to tumor for an individual liver cancer patient while maintaining the same estimated risk of liver complication for all patients (Ben Josef 2005). Using such an approach, an iso-toxic RT schedule that allows patients with HCC unsuitable for standard therapies to be treated in 6 fractions over two weeks using SBRT was developed at Princess Margaret Hospital (PMH), University of Toronto (Dawson 2006). The dose per fraction was determined based on the effective volume of normal liver irradiated (Veff), accounting for changes in dose per fraction compared to the original NTCP model. When the effective liver volume irradiated was low (Veff < 25%), doses of 54 Gy (9 Gy x 6) were delivered safely to HCCs, with excellent local control. For patients requiring higher volumes of liver to be irradiated (Veff 25-80%), doses from 24 to 54 Gy (4 to 9 Gy x 6) were delivered safely, although local control was reduced. The majority of first 31 Child-Pugh A HCC patients who completed 6 fraction SBRT (med 36 Gy, 24 – 54 Gy, 6 fractions) in the phase I study (14 - Hepatitis B; 12 - Hepatitis C; 4 - alcoholic liver cirrhosis) had main or main branch portal vein tumor thrombosis. No classic RILD was observed. Eight patients had grade 3 liver enzymes three months following therapy (3 with preexisting grade 3 liver enzymes), and there was no treatment-related grade 4/5 toxicity within 3 months following SBRT. Five patients had a decline in Child-Pugh score 3 months after SBRT (mostly in the presence of progressive HCC). One patient developed grade 3 thrombocytopenia. One year actuarial local control was 65% (95% CI 44-79%) and median survival was 11.7 months (95% CI 9.2-15.0 months). The median survival of the patients without portal vein thrombosis was 17.2 months (95% CI: 9-22.5 months) (Tse 2008). These results are encouraging since all patients had HCC refractory to prior therapy (66%) or were unsuitable for other standard therapies (34%). The most common site of first recurrence was in the liver outside the irradiated volume, providing rationale for studies combining regional or systemic therapies with SBRT.

An updated analysis of the completed phase I and II Toronto SBRT studies of 102 Child-Pugh A HCC patients ineligible for local-regional therapies (38% Hepatitis B, 38% Hepatitis C, 25% alcohol; 55% portal vein thrombosis; 12% extrahepatic disease) treated with SBRT (median dose 36 Gy in 6 fractions) from 2004 to July 2010 found a median survival of 17.0 months. A dose response for local control was observed (Bujold 2013).

1.5 Rationale for Sorafenib and Radiation Therapy

There is evidence of benefit from the combination of a variety of anti-angiogenic agents with radiation therapy at the pre-clinical level. Numerous pre-clinical models have documented improved outcome with the combination of RT and bevacizumab, PTK787, ZD6474, SU -11248, -11657, -5416 and -6668, angiostatin, thrombospondin-1, antibody mediated blockade of VEGFR2 (DC101 – mouse, and cp1C11 – human), blockade of alphaV/beta3 integrin signaling, and vascular disrupting agents (e.g. combretastatin, ZD6126, DMXAA) (Wilhelm 2004, Chang 2007, Winkler 2004). In addition, increasing the oxygenation of tumors with Sorafenib is expected to

improve the therapeutic ratio of radiation therapy to HCC. Sorafenib possesses dual antitumor activity by inhibiting the MAPK/ERK pathway and inhibiting neovascularization (Jain 2000). Sorafenib has been shown to inhibit proliferation and induce apoptosis in two HCC lines in vitro while also inhibiting tumor growth in an in vivo model (Liu 2006).

Another publication assessed combination treatment in a number of cell lines in vitro and HCT116 human colorectal xenografts in a subcutaneous flank model in nude mice (Plastaras 2007). Their data show that radiation followed by sorafenib appears to result in optimal anti-cancer effect compared to the concurrent administration of pre-treatment with sorafenib.

1.6 Clinical Experience with Sorafenib and Radiation Therapy (27Oct2017)

Although there is rationale to combine local therapies with sorafenib in HCC, there are few clinical publications on the combination of Sorafenib or similar agents with RT. One retrospective review of 23 patients from Taiwan with advanced HCC treated with RT and sunitinib (a TKI with similar mechanisms as sorafenib) has been published (Chi 2010). Sixty percent of patients had two or more lesions and 22% had extrahepatic disease. All were unresectable and unsuitable for transhepatic chemo-embolization (TACE). Five patients had major portal vein thrombosis. Fifteen patients had Child-Pugh score A; 8 were Child-Pugh B. All patients received sunitinib (25 mg) at least 1 week before, during, and 2 weeks after radiation therapy. Thirteen patients continued maintenance sunitinib after RT until disease progression. The median radiation dose was 52.5 Gy in 15 fractions. The objective response rate was 74%. The 1-year survival rate was 70%, with a median survival of 16 months. Maintenance sunitinib was the most significant factor for survival. The time to progression was 10 months in the maintenance group compared with 4 months in the control group. There were three episodes of upper gastrointestinal bleeding and one episode of pancreatitis. Ten patients had grade 2 or more elevation of liver enzymes, and 15 developed grade 2 or more thrombocytopenia. The authors concluded that conformal hypofractionated RT and sunitinib can be delivered safely in HCC patients.

Another phase I study investigated concurrent sunitinib (25 – 35.7 mg) and 10 fraction conformal radiation therapy (40 – 50 Gy in 10 fractions) in 21 patients with 36 sites of oligometastases in various locations, including the liver (n=9). No dose limiting toxicity was seen when sunitinib was delivered prior to, during and following RT (Chi 2010).

Phase I studies of sorafenib and RT for liver cancer have been conducted at PMH, Toronto. In one phase I study of 30 Gy in 10 fractions combined with escalating dose sorafenib prior to, during, and following RT, no dose limiting toxicity (DLT) was observed in patients with locally advanced HCC, several with massive portal vein thrombosis (Murray 2017)). Two other phase I studies of six-fraction SBRT plus escalating dose sorafenib were conducted at PMH (Ng 2016, Goody 2017). One study was for patients with liver metastases, and the other was for patients with HCC. Both studies combined SBRT (6 fraction) with sorafenib delivered 7 days pre-RT, during RT and post RT (1 week for metastases and continuous for HCC), to maximize RT sensitization by increasing tumor oxygenation, to increase the antitumor activity via the MAPK/ERK pathway and by inhibiting neovascularization that may occur post RT. Fifteen patients with focal liver metastases were evaluable for toxicity (3 at dose level 200 mg po bid, 6 at dose level 600 mg po od and 6 at 800 mg po od for 4 weeks), with no DLT. Twelve evaluable patients with HCC were treated on study, with continued sorafenib post SBRT. There was no DLT in three evaluable HCC patients treated with SBRT with a low effective liver volume (Veff 30%) combined with 400 mg sorafenib po od. In patients with a liver Veff of 30-60%, 2 of 3 evaluable patients treated with sorafenib 400 mg po daily developed DLT (grade 4 small bowel obstruction and grade 3 GI bleed); thus sorafenib was de-escalated to 200 mg po daily. One of 6 evaluable patients at this dose level developed DLT (tumor rupture). For the present study, the maximal permitted RT doses to the normal tissues have been reduced, compared to the above studies, and sorafenib will be delivered following RT (rather than concurrently with RT), to reduce the risk of toxicity.

1.7 Quality of Life (QOL)

1.7.1 QOL Overview

Quality of life (QOL) in HCC is understudied, but clearly of importance due to the expected poor overall survival in patients with advanced HCC, the co-morbidities that exist in these patients, the near universal presence of underlying liver disease and the potential for serious toxicity to occur from treatment.

There are few published prospective studies using validated questionnaires to assess longitudinal QOL in patients with HCC receiving local or systemic therapies. Ringash et al reported (in abstract) on prospective QOL assessment in liver metastases and HCC patients receiving SBRT using the FACT-Hep (Ringash 2008). In this phase I/II study of SBRT for unresectable liver cancers (35% HCC), QOL using the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) was collected at baseline, and at 1, 3 and 6 months post-treatment. Following SBRT, there was a trend for a decrease in QOL at 3 months; however, QOL at 6 months recovered in patients who were alive at that timepoint, suggesting a possible beneficial effect.

Due to the paucity of QOL data in HCC and the potential benefit of localized SBRT on QOL, it will be important to measure differences in health-related QOL in HCC patients treated with Sorafenib as compared to SBRT followed by Sorafenib on this trial. If SBRT is associated with a sustained reduction in the burden of HCC compared to sorafenib alone, it may lead to improved QOL compared to sorafenib alone.

1.7.2 Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep)

The FACT-Hep version 4 questionnaire will be used to measure QOL. The FACT-Hep is a 45-item self-report instrument designed to measure health-related quality of life (HRQL) in patients with hepatobiliary cancers. The FACT-Hep is validated and presents good internal consistency, test–retest reliability, and convergent and discriminate validity in patients with hepatobiliary cancer and HCC (Heffernan 2002, Steel 2006, Wang 2007, Steel 2004). The validity of FACT-Hep has recently been examined in a randomized controlled trial of an EGFRi or placebo (Cella 2012) In this study, FACT-Hep scores showed significant decline for progressive disease versus stable disease (e.g. difference in FACT-Hep total score -12.58; p = 0.004).

1.7.3 EuroQol (EQ-5D)

Patient-reported outcomes (PROs) are increasingly being incorporated into clinical trials for documentation of effects of treatment not measured by traditional endpoints, such as overall survival. This is important with interventions that may increase treatment-related side effects without positively impacting survival. Quality-adjusted survival is an endpoint that incorporates a patient's utility or preference of the health state that is combined with the time spent in that health state (Glasziou 1990).

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

The EQ-5D will be used to evaluate the effect of the addition of SBRT to sorafenib on quality-adjusted survival in this trial.

1.8 Biomarkers in HCC

1.8.1 Liver Toxicity

The possibility for liver toxicity to occur following therapy for HCC limits the effectiveness of therapies for HCC, especially for patients with locally advanced HCC. Sinusoidal obstructive syndrome is thought to be an important component of radiation induced liver disease; however the exact pathophysiology has not been clearly elucidated. As children who develop veno-occlusive disease (VOD) following transplant develop significant increases in plasminogen activator inhibitor type I, tissue plasminogen activator, and D-dimer and significant decreases in prothrombin time, antithrombin, and α2-antiplasmin at the time of their clinical diagnosis of veno-occlusive disease (VOD), such factors may be useful for better understanding radiation (or sorafenib) induced liver sinusoidal obstructive syndrome related toxicity.

In addition, transforming growth factor- ß is an important cytokine associated with tissue injury and wound healing and may be associated with non-specific liver disease, including cirrhosis, chronic hepatitis, or toxicity, from sorafenib or radiation. Other cytokines participate in the response to tissue injury, including proinflammatory cytokines IL-1-beta, IL-6, and tumor necrosis factor alpha. Baseline levels and temporal variations in levels of these cytokines may provide insight to liver toxicity pathogenesis, and may also be related to patient reported fatigue and decline in QOL.

1.8.2 Prognostic Factors

HCC specimen microvessel density (MVD), pERK (marker of signal transduction), VEGFR-2 (marker of angiogenesis) and Ki-67 and MIB-1 (markers for proliferation) are potential prognostic markers in HCC.

Circulating VEGF, soluble sVEGFR-s, Ang-1, Ang-2, PDGF, and sc-Kit have been correlated with sorafenib treatment response. Investigating changes in such potential biomarkers in a randomized trial may help to validate which biomarkers are most treatment predictive and/or prognostic.

1.9 Protocol Overview

A randomized phase III study of sorafenib versus SBRT followed by sorafenib for locally advanced HCC (unsuitable for or refractory to surgery, RFA or TACE) is proposed. It is expected that the primary patient population will have BCLC stage C HCC, due primarily to tumor vascular thrombosis. The sequential timing of treatments in the experimental arm (SBRT followed by sorafenib), rather than concurrent sorafenib and SBRT, should reduce the risk of toxicity. The dose of sorafenib during the first 28 days following SBRT is half standard dose (200 mg po bid) based on the Toronto phase I experience to reduce potential increase in toxicity due to radiation sensitization that may occur during that time period following SBRT. The primary endpoint is overall survival, and the hypothesis is that SBRT followed by sorafenib will improve survival in HCC patients by improving hepatic and vascular control of HCC, compared to sorafenib alone.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine if SBRT improves overall survival in HCC patients treated with Sorafenib

2.2 Secondary Objectives

2.2.1 To determine the difference in time to progression (TTP) and progression-free survival (PFS) in HCC patients treated with Sorafenib compared to SBRT followed by Sorafenib

2.2.2 To measure differences in toxicity in HCC patients treated with Sorafenib versus SBRT followed by Sorafenib

2.2.3 To measure vascular thrombosis response post Sorafenib versus SBRT followed by Sorafenib

2.2.4 To measure differences in Health Related QOL and quality-adjusted survival in HCC patients treated with Sorafenib compared to SBRT followed by Sorafenib

2.2.5 Collection of biospecimens for future correlative studies to investigate differences in potential biomarkers in patients treated with Sorafenib versus SBRT followed by Sorafenib

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (13-MAY-2019)

For questions concerning eligibility, please contact Data Management or the Study Chair (see second page of protocol).

3.1.1 Patients must have an HCC diagnosis (initial, recurrent, progressive and/or refractory to other therapies) by at least one criterion listed below ≤360 days prior to study entry

a) Pathologically (histologically or cytologically) proven diagnosis of HCC.

b) At least one solid liver lesion or vascular tumor thrombosis (involving portal vein, IVC and/or hepatic vein) > 1 cm with arterial enhancement and delayed washout on multi-phasic computerized tomography (CT) or magnetic resonance imaging (MRI) in the setting of cirrhosis or chronic hepatitis B or C without cirrhosis.

c) For patients whose CURRENT disease is vascular only:
Enhancing vascular thrombosis (involving portal vein, IVC and/or hepatic vein) demonstrating early arterial enhancement and delayed washout on multi-phasic CT or MRI, in a patient with known HCC (diagnosed previously < 720 days), using criteria in 3.1.1a or 3.1.1b

3.1.2 Patients must have measureable hepatic disease and/or presence of vascular tumor thrombosis (involving portal vein, IVC and/or hepatic vein) which may not be measureable as per RECIST, as defined in Section 11.0) on liver CT or MRI, within 28 days PRIOR TO STUDY ENTRY

3.1.3 Appropriate for protocol entry based upon the following minimum diagnostic workup:

- History/physical examination including examination for encephalopathy, ascites, weight, height, and blood pressure within 14 days prior to study entry
- Assessment by radiation oncologist and medical oncologist or hepatologist who specializes in treatment of HCC within 28 days prior to study entry.
- **Pre-randomization Scan (REQUIRED for All Patients):** Within 28 days prior to study entry, multiphasic liver CT or multiphasic liver MR scan-. **See Appendix V and Section 4.1.7 for details.**
- Within 28 days prior to study entry CT chest with CT or MR abdomen and CT or MR pelvis, or PET CT chest/abdomen/pelvis-.

3.1.4 Zubrod Performance Status 0-2 within 28 days prior to study entry

3.1.5 Age ≥ 18

3.1.6 All blood work obtained within 14 days prior to study entry with adequate organ marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
- Platelets ≥ 60,000 cells/mm^3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)
- AST and ALT < 6 times ULN
- Serum creatinine ≤ 2 x ULN or creatinine clearance ≥ 60 mL/min

3.1.7 Patients must have BCLC stage: Intermediate (B) or advanced (C) (see Appendix IV) within 28 days prior to study entry

3.1.8 Child-Pugh score A within 14 days prior to study entry (using INR from < 28 days is acceptable)

3.1.9 Women of childbearing potential and male participants must agree to practice adequate contraception while on study and for at least 6 months following the last dose of RT and for at least 28 days following the last dose of sorafenib (whichever is later).

3.1.10 Unsuitable for resection or transplant or radiofrequency ablation (RFA)

3.1.11 Unsuitable for or refractory to transarterial hepatic chemo-embolization (TACE) or drug eluting beads (DEB) for any of the following reasons, as described by Raoul et al (2011):

- Technical contraindications: arteriovenous fistula, including surgical portosystemic shunt or spontaneous portosystemic shunt

- Severe reduction in portal vein flow: due to tumor portal vein, IVC or atrial invasion or bland portal vein occlusion
- Medical contraindications including congestive heart failure, angina, severe peripheral vascular disease
- Presence of extrahepatic disease
- No response post TACE (or DEB) or progressive HCC despite TACE. Prior TACE or DEB is allowed but must be > 28 days from study entry
- Serious toxicity following prior TACE (or DEB). Prior TACE or DEB must be > 28 days from study entry
- Other medical comorbidities making TACE (or DEB) unsafe and/or risky (e.g. combination of relative contraindications including age > 80 years, tumor > 10 cm, > 50% replacement of the liver by HCC, extensive multinodular bilobar HCC, biliary drainage)

3.1.12 Patients treated with prior surgery are eligible for this study if they otherwise meet eligibility criteria.

3.1.13 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (27Oct2017)

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer and T1 renal cell carcinoma) unless disease free for a minimum of 2 years (Note that carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible)

3.2.2 Prior sorafenib use > 60 days and/or grade 3 or 4 Sorafenib related toxicity. Note that prior chemotherapy for HCC or a different cancer is allowable. See Section 3.2.1.

3.2.3 Prior radiotherapy to the region of the liver that would result in excessive doses to normal tissues due to overlap of radiation therapy fields

3.2.4 Prior selective internal radiotherapy/hepatic arterial Yttrium therapy, at any time

3.2.5 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months PRIOR TO registration
- Transmural myocardial infarction within the last 6 months prior to study entry
- Unstable ventricular arrhythmia within the last 6 months prior to study entry
- Acute bacterial or fungal infection requiring intravenous antibiotics within 28 days prior to study entry
- Hepatic insufficiency resulting in clinical jaundice, encephalopathy and/or variceal bleed within 28 days prior to study entry
- Bleeding within 28 days prior to study entry due to any cause, requiring transfusion
- Thrombolytic therapy within 28 days prior to study entry. Subcutaneous heparin is permitted.
- Known bleeding or clotting disorder
- Uncontrolled psychotic disorder

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

3.2.7 Maximal diameter of any one hepatocellular carcinoma > 15 cm

3.2.8 Total sum of maximum diameters of each definite parenchymal hepatocellular carcinoma within the liver or maximum diameter of a single conglomerate HCC > 20 cm

3.2.9 More than 5 discrete intrahepatic parenchymal foci of definite HCC

3.2.10 Direct tumor extension into the stomach, duodenum, small bowel or large bowel

3.2.11 Measureable common or main branch biliary duct involvement with HCC

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

3.2.13 Prior liver transplant

3.2.14 HIV positive with CD4 count < (350) cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ (350) cells/microliter, and no known detectable viral load, at the time of study entry. Note also that HIV testing is not required for eligibility for this protocol

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (27OCT2017)

4.1.1 Assessment of degree of vascular involvement (IVC, main portal vein, right or left main branch portal vein versus other vascular involvement (e.g. peripheral portal branches, hepatic vein) versus none). See Appendix X for details.

4.1.2 Documentation of liver disease, including cirrhosis, Hepatitis history [Hepatitis B and Hepatitis C status, hemachromatosis, alcohol, autoimmune disease, non-alcoholic steatohepatitis (NASH)]

4.1.3 Alfa-feto protein (AFP) within 28 days prior to study entry

4.1.4 Bilirubin, INR, albumin, alkaline phosphatase (ALP), phosphate, sodium, potassium, chloride, magnesium, calcium within
28 days prior to study entry

4.1.5 bHCG within 14 days prior to study entry if patient is pre or peri menopausal

4.1.6 Documentation of any extrahepatic disease status, number of sites and sum of maximum diameter of extrahepatic disease

4.1.7 Submission of IV contrast diagnostic or planning CT or MRI scan **(See Section 3.1.3)** within 1 week of randomization for patients not randomized to SBRT (**Note**: This scan is used for the stratification factors of tumor:(liver [including all GTV]) ratio and the degree of vascular thrombosis, so the actual scan and measurements should be done as close to the time of study entry as possible.).

For all patients, this scan should include:

- Multiple phases of imaging if needed to best demonstrate the GTV (e.g. arterial, venous and delayed)
- Contours of GTV (gross tumor volume = volume of all parenchymal and vascular HCC)
- Contours of the liver (whole liver including GTV)

4.2 Highly Recommended Evaluations/Management (27Oct2017)

Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

4.2.1 Consultation by hepatologist within 28 days prior to study entry (strongly recommended if known Hepatitis B or C and/or the patient has never seen a hepatologist)

4.2.2 Work-up for Hepatitis B and Hepatitis C within 28 days prior to study entry (if Hepatitis status not previously documented)

4.2.3 Patients with known portal hypertension or known history of varices should have an endoscopic assessment of and appropriate treatment of varices within 6 months of study entry

4.2.4 Calculation of MELD score within 14 days prior to study entry (Appendix VII)

4.2.5 Assessment of vascular thrombosis (tumor thrombosis [e.g. with arterial enhancement and venous phase washout on CT or MRI] or bland thrombosis)

4.2.6 Documentation of prior HCC therapies

4.2.7 Documentation of any liver disease etiology and any other factors associated with liver disease

4.2.8 Initiation of treatment of viral Hepatitis B (if untreated) prior to study therapy, to be done under the supervision of hepatology

4.2.9 If randomized to SBRT, consultation with interventional radiology or surgery for possible fiducial marker insertion and/or tissue expander placement to move tumor away from luminal GI structures if this is estimated to benefit the patient and center has expertise in these procedures.

4.2.10 If randomized to SBRT, and stomach or duodenum is within irradiated volume (> 20 Gy), proton pump inhibitors are highly recommended to reduce the risk of SBRT related GI bleeding.

4.2.11 If medically appropriate, discontinuation of regular (daily) phenytoin, carbamazepine, phenobarbital or dexamethasone

4.2.12 For all patients, the following criteria calculated from baseline CT or MR scans (see Section 4.1.7) should be met:

- Liver volume minus intrahepatic GTV > 700 cc.
- Intrahepatic GTV/[liver volume (including the intrahepatic GTV)] ratio <80%.

5.0 REGISTRATION, STUDY ENTRY PROCEDURES (23-SEP-2022)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Add to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), or consenting/treating/drug shipment investigator in OPEN must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm . For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

5.1 Pre-Registration Requirements for all Radiation Techniques (27Oct2017)

In order to be eligible to enroll patients onto this trial, the center must be credentialed for SBRT. See the credentialing table for details. SBRT credentialing consists of liver image-guided radiotherapy (IGRT) credentialing, as described in Section 5.2 below. An additional component of the SBRT credentialing is the completion of the IGRT questions in Parts II and III of the Facility Questionnaire (see Section 5.1.3). If IMRT or protons are to be used, the center must be credentialed for these treatment modalities (see Sections 5.3 and 5.4). Institutions using only 3D conformal delivery techniques must follow the same credentialing approach described for IMRT. Institutions using either 3D-CRT or IMRT need to be credentialed for IMRT only. Based on the answers to the questions in Part III of the Facility Questionnaire, the phantom provided for IMRT, 3D-CRT or proton credentialing will come with a moving table when either gating or tracking are used for motion management. Irradiation of an anthropomorphic phantom on a moving table, when dictated by the motion management technique, is the final part of the SBRT credentialing.

RT Credentialing Requirements	**Web Link for Procedures and Instructions: http://irochouston.mdanderson.org**			
	Treatment Modality			Key Information
	SBRT	IMRT	Proton	
Facility Questionnaire	✓	✓	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	✓	✓	✓	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Benchmark	✓	✓	✓	The benchmark case is to be downloaded and completed by the site before submission to a QA center.

Cases				http://atc.wustl.edu/protocols/rtog/1112/1112.html
Phantom Irradiation	✓	✓	✓	A liver phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that only the most sophisticated technique needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used. Tomotherapy, Cyberknife and proton treatment delivery modalities must be credentialed individually. The motion management technique must be used during phantom irradiation. Acceptable TPS/ algorithm must be used.
IGRT Verification Study	✓	✓	✓	The institution must submit a sample of verification images showing their ability to reproducibly register daily IGRT information with a planning CT dataset (i.e., the GTV falls within the CT simulation defined PTV). The patient ("as if patient") used for this study must have a target (or mock target) in the liver. The information submitted must include 2 IGRT datasets (from 2 treatment fractions) for a single patient and must employ the method(s) that will be used for respiratory control for patients entered from a particular institution (e.g. abdominal compression, breath hold, etc…). This information with a spreadsheet (the spreadsheet is available on the IROC Houston web site, http://irochouston.mdanderson.org
Institution				IROC Houston QA Center will notify the site that all desired credentialing requirements have been met. The site will need to upload a PDF of the approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated.

5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information may enter patients onto this study. All proton facilities must have completed baseline approval steps in addition to credentialing steps.

5.1.2 **IROC Houston will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.**

General Radiation Credentialing Process

The following are required for all techniques, including conformal non-IMRT, non-proton SBRT:
A **liver phantom study** provided by the Imaging and Radiation Oncology Core (IROC) Houston (formerly Radiological Physics Center [RPC])], must be successfully completed. Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org. See the credentialing table for details; select "Credentialing" and "NRG Oncology". Upon review and successful completion of the phantom irradiation, IROC will notify both the registering institution and NRG Oncology that the institution has completed this requirement. Subsequently, NRG Oncology will notify the institution that the site can enroll patients on the study. Note that only the most sophisticated technique needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used.

Each participating institution also must successfully complete and submit a protocol-specific **Benchmark Plan ("Dry-Run" QA)**. The Benchmark Scan will be made available for downloading from IROC: (http://atc.wustl.edu/protocols/rtog/1112/1112_benchmark.html). See the credentialing table for details. The scan should be contoured and planned as per RTOG 1112. The completed benchmark case will be submitted to TRIAD and selecting "benchmark" on the drop down menu. The benchmark target contour, normal tissue contour and dosimetry will be

reviewed by the PI or her designee, who will notify IROC if the institution has successfully completed this requirement. Feedback will be provided to the participating institution.

5.2 Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT) (27OCT2017)

5.2.1 IGRT is required in this protocol and the center must be credentialed for its use. This means the institution must have met technology requirements and have provided the baseline physics information. This information is available at: http://irochouston.mdanderson.org on the 1112 protocol page. See the credentialing table for details.

5.2.2 IGRT Credentialing Process

The institution must submit a sample of verification images demonstrating their ability to reproducibly register daily IGRT information with a planning CT dataset (i.e., the GTV falls within the CT simulation defined PTV). See the credentialing table for details. A soft tissue surrogate for the GTV (e.g. liver, TACE cavity, inserted fiducial markers) must be used for alignment. Boney anatomy should not be used for alignment. The patient ("as if patient") used for this study must have a target (or mock target) in the liver. The information submitted must include 2 IGRT datasets (from 2 treatment fractions) for a single patient and must employ the method(s) that will be used for respiratory control for patients entered from a particular institution (e.g. abdominal compression, breath hold, etc). This information with a spreadsheet (the spreadsheet is available on the web site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1112) will be reviewed by the Physics Co-Chair, assisted by IROC Phila RT. Upon approval of the images and spreadsheet, IROC Phila RT will notify the institution that it is credentialed to use IGRT. Pre-treatment images may include three-dimensional (3D), 4-dimensional (4D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (kV) x-ray) or paired kV 2D images. 2D MV images are not permitted to be used as the only tool for IGRT. These images and the spreadsheet will be reviewed by the physicist PI or designee. Each different combination of IGRT technology and motion management technology should be credentialed in this manner; centers will receive feedback from this IGRT credentialing. Registration of the first patient to the protocol cannot proceed until approval for the "as if patient" is obtained.

For each IGRT technology, in addition to each "as if patient" dataset, the images for all treatment fractions and offsets for the first two actual patients treated with SBRT on study should be submitted for review within 5 days of completion of therapy. Feedback will be communicated to the participating institution regarding IGRT credentialing.

5.3 Pre-Registration Requirements for Intensity Modulated Radiation Therapy (IMRT) (27Oct2017)

5.3.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the IROC Houston web site. See the credentialing table for details.

5.3.2 If IMRT is to be used, review and successful completion of the **Benchmark Plan** (**"Dry-Run" QA** test) using IMRT is required, NRG Oncology will notify the registering institution that the institution has successfully completed this requirement for IMRT.

5.3.3 Participating institutions must use approved heterogeneity algorithms by IROC. Acceptable choices of algorithm are listed at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf

5.3.4 Sites using CyberKnife™ equipment must be credentialed for dose painting IMRT prior to enrolling patients on study. See the credentialing table for details.

5.3.5 If an institution is credentialed for the use of IMRT on this study, this IMRT credentialing for the specific treatment modality will suffice for non-IMRT photon treatment delivery. As such the institution will not have to re-credential for non-IMRT photon treatment delivery.

5.4 Pre-Registration Requirements for Proton Treatment Approach (25-MAR-2020**)**

5.4.1 Proton Credentialing Process

Proton therapy may be used on this protocol. Investigators using proton therapy must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the websites of the RPCIROC Houston (http://irochouston.mdanderson.org), and. These requirements include, but are not limited to, completion of a proton facility questionnaire, a successful IROC Houston site visit, which identifies the proton technique(s) which can be used, annual monitoring of the proton beam calibration, e.g. IROC Houston's monitoring program, and having established TRIAD account for submission of digital data.

5.4.2 Dose will be reported in Gy (RBE), where 1 Gy(RBE) = proton dose Gy x RBE (radiobiological effective dose), RBE = 1.1.

5.4.3 Radiation doses shall be prescribed using the protocol specified definitions for GTV and CTV. For set-up uncertainties and target motion, additional margin (including proximal and distal), smearing, and range of modulation will be added on a per beam basis. Proton treatment plans will be based upon a CT scanner for which the institution has defined an imaging protocol for protons which establishes the relationship between the CT number and the stopping power ratios.

5.4.4 The IROC Houston will coordinate the completion of the proton therapy use approval process in conjunction with the appropriate other Quality Assurance Offices for any additional protocol specific credentialing requirements. A specific proton liver phantom study provided by IROC Houston must be successfully completed (if the institution has not previously met this credentialing requirement for proton therapy). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select "Credentialing" and "NRG Oncology". Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed this requirement. Subsequently, NRG Oncology will update the RSS database when all credentialing requirements have been met.

5.4.5 Proton resources for this protocol include:

Medical Physics Co-Chair (Protons)
Michael T. Gillin, PhD
Professor
The University of Texas
MD Anderson Cancer Center
Department of Radiation Physics
Phone: 713-563-2507/Fax: 713-563-2545
mgillin@mdanderson.org

Radiation Oncology Co-Chair (Protons)
Sunil Krishnan, MD
Mayo Clinic Florida
Dept. of Radiation Oncology
4500 San Pablo Road
Jacksonville, FL 32224-1865
904-953-2000
krishnan.sunil@mayo.edu

5.4.6 If protons are to be used, review and successful completion of the **Benchmark Plan** (**"Dry-Run" QA** test) using protons is required, the IROC Houston will notify both the registering institution and NRG Oncology that the institution has successfully completed this requirement for protons.

5.5 Digital Radiation Therapy Data Submission Using Transfer of Images and Data (26-MAY-2022)

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

TRIAD Access Requirements:

- A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

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

TRIAD Installation:

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

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

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

5.6 Regulatory Pre-Registration Requirements (23-SEP-2022)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

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

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Protocol Specific Requirements

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site any roster is required can to update the provider associations, though all individuals at a site may view provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link section on the CTSU website.

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

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

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and IRB/REB approved consent (applies to International and Canadian sites only: English and native language versions*****)

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

- Credentialing documentation received from IROC Houston must be uploaded to the CTSU Regulatory Portal for RSS to be updated.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.

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

Downloading Site Registration Documents:

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

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG* and protocol number RTOG-1112
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-CTSU 2878 in order to receive further instruction and support.

Checking Site's Registration Status:
Site's registration status may be verified on the CTSU members' website.

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

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for

individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines [per section 6.2.5 of ICH E6(R2)]. This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, essential documents must be retained for 25 years following the completion of the trial at the participating site (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by the sponsor, NRG Oncology, that documents no longer need to be retained [per C.05.012 (4) of the FDR]. In addition, upon request by the auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access [per section 4.9.7 of ICH]. Prior to clinical trial commencement, Canadian institutions also must complete and submit the following documents to the CTSU Regulatory Office via the Regulatory Submission Portal:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

For institutions that have not been approved for this protocol, please contact NRG Headquarters for approval.

5.7 OPEN Registration (13-MAY-2019)

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

Oncology Patient Enrollment Network (OPEN)

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

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

5.7.2 In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY 19-AUG-2019

Notes: See Section 5.5 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

IMRT, SBRT, and Protons are allowed. The rationale for protons includes their ability to limit the dose to normal tissue, including the non-GTV liver tissue.

For patients randomized to the SBRT arm, SBRT is to be delivered over 5 fractions delivered over 5 to 15 days followed by Sorafenib.

For patients who are taking sorafenib prior to randomization to SBRT (<60 days as per eligibility), the sorafenib is recommended to be held at least 2 to 5 days prior to the start of SBRT, and should not be delivered concurrently with SBRT.

This protocol requires, at a minimum number, **pre-treatment review of the contours and plan PRIOR TO DELIVERY of radiation treatment for the first three registered patients**. More pre-treatment reviews will be required if deviations are seen in these reviewed plans. These pre-treatment reviews are aimed at providing feedback from the co-chairs and IROC on the institution's imaging, contours and treatment plan. In order to accomplish these reviews, digital data must be submitted in a rapid fashion. Three business days are required to complete a pre-treatment review. The 3 days start once complete data has been received. Feedback for the first registered patient must be received before the second patient is registered, and feedback for the second patient must be approved before the third patient is registered. Following approval of a minimum of three cases (in addition to the benchmark case described in Section 5.1.5), all subsequent cases will undergo a timely review. Thus, digital data must be submitted in a timely fashion for all plans. Data submission for a timely review must be within 5 days of completion of radiation therapy. Based on the results of any of the reviews described above, a request for additional rapid reviews might be necessary.

A liver protocol CT (Appendix V) must be obtained for treatment planning.

Protocol treatment is encouraged to begin as soon as possible after study entry. Protocol treatment must begin within 21 days after study entry unless extra time is needed for fiducial marker insertion, but not to exceed 28 days.

6.1 Dose Specifications (27Oct2017)

6.1.1 The primary tumor(s) and any tumor vascular thrombi must be treated. Prophylactic nodal radiation is not permitted. Treatment of non-tumor extrahepatic vascular thrombi, RFA cavities and prior TACE sites is not recommended unless the treating oncologist believes these regions are at high risk of containing microscopic HCC (e.g. HCC growing from a RFA cavity) and normal tissue limits can be maintained.

6.1.2 Treatment Schedule: Treatment will be delivered in 5 fractions. The time between fractions should be between 24 and 72 hours, with treatment delivered to all targets over 5 to 15 days (with 10 days being the preferred treatment time). The preferred inter-fraction interval is 48 hours. All lesions may be treated on the same day, or alternative lesions may be treated on alternate days, as long as the overall treatment time is 15 days at maximum. When there are multiple target volumes, a composite plan demonstrating the composite doses to the targets, liver and other normal tissues must be submitted, and all planning guidelines must be met, as described in Section 6.5 (i.e. individual target plans are not to be submitted separately).

6.1.3 Prescription Dose

Photons: Absorbed dose: 27.5 Gy - 50 Gy in 5 fractions. The prescription dose may be 50 Gy, 45 Gy, 40 Gy, 35 Gy, 30 Gy or 27.5 Gy in 5 fractions, based on normal tissue constraints. The dose to multiple PTVs may be different. The goal is to use the highest allowable prescription dose to the primary target, while respecting normal tissue constraints. The minimal planned prescription dose to PTVs is 27.5 Gy.

Protons: Absorbed dose: Doses are expressed in units of RBE-weighted absorbed dose, D_{RBE}. For protons the RBE is taken to be 1.1. $D_{RBE} = 1.1 \times D$, where D represents the absorbed dose in Gy.

Absorbed dose D_{RBE} 27.5 Gy – 50 Gy in 5 fractions, with the prescription dose 50 Gy (RBE), 45 Gy (RBE), 40 Gy (RBE), 35 Gy (RBE), 30 Gy (RBE) or 27.5 Gy (RBE) in 5 fractions, based upon normal tissue constraints. The minimal planned prescription dose to PTVs is 27.5 Gy (RBE).

6.1.4 Dose Specifications

Photons: The prescription isodose should encompass 95% of PTV. The dose to multiple PTVs within the same patient may vary. If there are multiple PTVs, each should be planned for one of the prescription doses listed above, with each specific covering isodose planned to encompass 95% of each PTV, with normalization to the PTV receiving the highest dose. **The highest allowable doses to the target volumes that maintain normal tissue constraints should be used.** A goal is that 100% of the CTV is encompassed by the prescription dose. The unit of dose is Gy.

Protons: The prescription isodose is planned to encompass 95% of the PTV. The dose to multiple PTVs within the same patient may vary. If there are multiple PTVs, each should be planned for one of the prescription doses listed above, with each specific covering isodose planned to encompass 95% of each PTV, with normalization to the PTV receiving the highest dose. The highest allowable doses to the target volumes that maintain normal tissue constraints should be used. A goal is that 100% of the CTV is encompassed by the prescription dose. The unit of dose is Gy(RBE).

6.1.5 Dose prescription: Is based on the volume of normal tissues irradiated (correlated with mean liver dose), as well as proximity of stomach, duodenum, small and large bowel (GI luminal structures) to the target volumes, as normal tissue constraints must be maintained in this study.

In the absence of adjacent GI luminal structures that may limit dose, the PTV dose prescription should be as high as possible based on mean liver dose (MLD, defined as the mean dose to the liver minus all GTVs), with 6 potential dose levels: Use of effective liver volume (Veff) to aid in dose allocation is permitted (Appendix X). If there are discrepancies in the Veff and MLD for the prescription dose allocation, MLD has priority. A call to the clinical PI or physics PI is recommended if this occurs.

Optional Constraint	**Priority Constraint**	**Prescription Dose**	
Liver Veff	Allowed Mean	Planned	If the maximum allowed MLD is exceeded

	Liver Dose [MLD] (Gy)	Prescription Dose (Gy)	at this planned dose
< 25%	13.0	50	Reduce to 45 Gy and re-evaluate
25 - 29%	15.0	45	Reduce to 40 Gy and re-evaluate
30 - 34%	15.0	40	Reduce to 35 Gy and re-evaluate
35 - 44%	15.5	35	Reduce to 30 Gy and re-evaluate
45 - 54%	16.0	30	Reduce to 27.5 Gy and re-evaluate
55 - 64%	17.0	27.5	Ineligible

Dose values in this table should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1).

- Vascular tumor thrombosis (e.g., portal vein or other vascular HCC thrombosis or invasion) should be considered GTV and treated as per 6.1.5. Non-tumor bland thrombosis is not recommended to be irradiated, but may be included as CTV (rather than GTV) if judged at risk of containing HCC.
- Maximum dose within PTV = 150%. If multiple PTVs exist, 150% of the maximal PTV prescription dose is permitted for all PTVs.
- Maximum dose outside PTV = 120% of the maximal PTV prescription.
- Efforts should be made to keep the prescription dose and the 30Gy isodose as conformal as possible.
- Different isodoses may cover different PTVs. If multiple PTVs, the MLD should be evaluated with the prescription dose corresponding to the highest dose level that any PTV is treated. Queries should be directed to the study PI, Dr. Dawson, or physics PI, Dr. Craig.

6.2 Technical Factors

6.2.1 Equipment (photons): Megavoltage equipment with photons of at least 6MV, capable of daily image guidance, with a multileaf collimator for intensity modulation is required. Inverse-planned IMRT, forward planned IMRT and conventional 3D CRT are permitted.
Equipment (protons): The proton delivery system must deliver protons of sufficient energy to cover the target. There is less integral dose with protons, which should reduce the risk of toxicity in patients with HCC.

6.2.2 CT based planning required. For non-proton plans, a minimum of 5 beam angles is strongly recommended. Arc therapy is permitted.

6.2.3 Image guided radiation therapy (IGRT): IGRT is mandatory.

6.2.4 Breathing motion management is recommended if breathing motion is > 5 mm. Breathing motion assessed on 4DCT and adequately treated with PTV margins < 20mm is permitted.

6.3 Localization, Simulation, and Immobilization (27Oct2017)

6.3.1 Custom immobilization is recommended (e.g. With vacuum immobilization, patient positioning boards, knee cushions, and/or breath hold immobilization with active breathing control).

6.3.2 Treatment planning CT scans will be required to define GTV. Multi-phasic IV contrast is recommended for the planning CT (arterial phase and/or delayed phase imaging recommended for GTV delineation, and venous phase for portal vein thrombosis delineation). If oral contrast is used at simulation, similar timing and volume of oral contrast is to be used at the time of treatment.

Exhale breath hold CT or average phase CT (from 4D CT) may be used as the baseline CT for radiation therapy planning. CT scans obtained during free breathing are strongly discouraged, but may be used if breath hold scanning is not possible for individual patients or if breathing motion is < 5 mm. CT scans used for target delineation are recommended to be multi-phase IV contrast scans obtained in breath hold. Exhale breath hold is preferred as it most often is closer to the average position than inhale breath hold, and exhale is more reproducible than inhale. If IV contrast scans cannot be obtained at the time of radiation planning, IV contrast CT scans from

diagnostic radiology can be imported to the planning system to aid in target delineation and fused to the primary planning dataset to aid in target definition.

Alternatively, an IV contrast multiphase liver MR may be used to define GTV.

All scans used for target delineation should be fused to each other so that the livers are registered to each other for target delineation. Registration will be performed with the best fit liver-to-liver image registration, focusing on the region of the PTVs if deformation or rotation occurs between scans. Imaging details are in Appendix V.

6.3.3 Breathing motion assessment. Measurement of target/liver breathing motion is required, unless breath hold is to be used for liver immobilization. Motion may be assessed using 4D CT, fluoroscopy and/or cine MR.

4D CT: A 4D, or respiratory sorted, CT may be obtained for assessing motion if breath hold is not used for liver immobilization.

Liver reproducibility of position in breath hold should be measured using fluoroscopy, CT or MRI.

6.3.4 Proton Specific Guidelines

Localization, Simulation, and Immobilization Guidelines

Patients must be simulated on a CT scanner, which has been commissioned for protons. Proton compatible immobilization devices are required, as is a motion management system. Immobilization devices will not extend to the lower thorax so as to minimize proton entrance through them. For contrast-enhanced CT simulations (either breath-hold or free-breathing), the initial CT sequence will be the non-contrast scan for proton planning purposes and the subsequent scan will be the contrast scan for contouring. All oral contrast Hounsfield units will be overridden during planning and replaced with a Hounsfield unit of 1. Hounsfield units for lipiodol, fiducials and clips will remain unchanged during planning. Where possible the proton beam will not exit into GI mucosa. Breathing motion management is recommended if breathing motion is > 5 mm. Breathing motion assessed on 4DCT and adequately treated with PTV margins < 20mm is permitted. Shadowing of dose along a beam behind radio-opaque fiducials is negligible and can be discounted during multi-beam proton planning. Where fiducials are used for breath-hold set-up, reproducibility of breathing amplitude on days of treatment compared to simulation will be confirmed prior to treatment delivery.

6.4 Treatment Planning/Target Volumes (27Oct2017**)**

6.4.1 The **Gross Tumor Volume (GTV) is defined as all parenchymal and vascular HCC** visualized on contrast enhanced CT and/or MRI, most often best seen on arterial phase (as hyperintensity) and/or venous or delayed phase (as hypointensity relative to liver). GTVp1 should represent the 'primary parenchymal (=p) dominant (=1)' GTV, upon which primary QA will be based. Subsequent lesions can be labeled as GTVp2, GTVp3, GTVp4 and GTVp5). If 'p' is not included following "GTV", the lesion will be assumed to be parenchymal. Vascular HCC thrombi (GTVv) most often are best seen on venous phase imaging as hypointensity relative to the contrast in the vessel, Vascular HCC may be combined with parenchymal HCC (labeled as GTVp or GTVpv) if they are to be treated to the same dose.

Non-tumor thrombi should not be considered as GTV; they should be excluded from contouring or may be included in the CTV (as per 6.4.2). Non-tumor extrahepatic vascular thrombi should not be treated as GTV or CTV.

Small enhancing GTV in adjacent lymph nodes are permitted to be irradiated only if normal tissue limits are not exceeded. They are not required to be irradiated, and no prophylactic nodal irradiation is allowed.

The prescription dose should be annotated to each GTV after the final plan is complete (e.g. GTVp1_50 for a 50Gy target).

Diagnostic contrast CT or MR imaging may be fused with the planning CT if there is no IV contrast used in the planning CT (liver-to-liver fusion is recommended).

6.4.2 The Clinical Target Volume (CTV): For each GTVp, the CTV is defined as the GTV (CTVp1… CTVp5), with no expansion. The minimal CTVv is the GTVv, with no expansion. **It is expected that there will be no expansion from GTV to CTV for the majority of cases.** However, CTV expansions to include regions at high risk for microscopic disease, including non-tumor vascular (v) thrombi (CTVv), prior TACE (t) sites (CTVt), or adjacent RFA (r) (or other ablation) sites (CTVr) are permitted. Such CTVs may be treated to a microscopic dose (27.5 Gy) or up to as high as the prescription dose, at the investigator's discretion. Separate CTVs should be labeled CTVp1, CTVv2, CTVv3, CTVt4…etc. The prescription dose should be annotated to each CTV after the final plan is complete (e.g. CTVp1_50 for a 50Gy target, and CTVt2_27.5 for a CTV treated to 27.5 Gy).

6.4.3 The Planning Target Volume (PTV)

The **Photon PTV** will provide a margin around each CTV to compensate for set-up and internal organ motion. PTV nomenclature should follow CTV nomenclature guidelines. For example, PTVv for the PTV around the CTVv and PTVp1 and PTVp2 for PTVs around CTVp1 and CTVp2. A minimum PTV margin of 4 mm around each CTV is required in all directions (for example if active breathing control is used with excellent reproducibility). The maximum permitted PTV margin is 20 mm, expected to be used uncommonly. **PTV margins ≤ 10 mm are a goal.** Asymmetric PTV margins are permitted. The actual PTV used will depend on motion management used, the patients' motion and reproducibility. **PTVs should not be manually modified due to proximity of adjacent OARs.** The final PTVs should have dose annotated once the plan is final. Eg. PTVp1_50 and PTVv1_27.50 for targets treated to 50 cGy and 27.5Gy, respectively.

The **Proton PTV** will provide a margin around each CTV to compensate for uncertainties including set-up and internal organ motion, aperture margin definitions, compensator smearing, range of individual beams, and modulation width of the SOBP. PTV nomenclature should follow CTV nomenclature guidelines, in a similar manner to the photon PTV. For example, PTVv_EN for the PTV around CTVv_EN. A minimum PTV margin of 4 mm around the CTV is required in all directions (for example if active breathing control is used with excellent reproducibility). The maximum permitted PTV margin is 20 mm. Asymmetric PTV margins are permitted, depending on institution motion management, individual patients' motion and reproducibility. The final PTVs should have RBE-weighted dose annotated once the plan is final. Eg. PTVp1_50 and PTVv1_27.5. Additionally, the effect of variations in the set-up of the target with respect to tissue inhomogeneities (e.g., employing compensator smearing technique, beam-specific PTV etc.), or range uncertainties (e.g., by expanding the prescribed range and modulation, to create distal and proximal field margins) should be addressed in the design of treatment fields for each beam direction.

As suggested in ICRU Report 78, paragraph 5.1.4.4, an adjustment must be made within the beam-design algorithm to take into account the margins needed to account for uncertainties along the beam direction (i.e. range uncertainties) and those included in the traditional PTV (i.e. lateral uncertainties). The proton distal target margin range will be determined as follows: Proton Distal Target Margin Range = distal aspect of the CTV + Range Calculation Uncertainty (generally 3.5%) + Set-up Margin + Internal Margin

6.4.4 Examples of target nomenclature

Examples	GTV	CTV	PTV
Parenchymal (p) HCC, prescription dose 50Gy	**GTVp1_50 Or GTV1_50 Or GTV_50**	**CTVp1_50 Or CTV1_50 Or CTV_50**	**PTVp1_50 Or PTV1_50 Or PTV_50**
Vascular (v) HCC thrombosis, prescription dose of 45Gy	**GTVv1_45**	**CTVv1_45**	**PTVv1_45**
Combined parenchymal and vascular HCC, prescription dose 45Gy	**GTVpv1_45 or GTVp1_45**	**CTVpv1_45 or CTVp1_45**	**PTVpv1_45 or PTVp1_45**

Nodal (n) HCC, prescription dose 35Gy	**GTVn2_35**	**CTVn2_35**	**PTVn2_35**
Combined primary (p) and TACE (t) site, prescription dose 30Gy	**GTVpt1_30 or GTVp1_30**	**CTVpt1_30 or CTVp1_30**	**PTVpt1_30 or PTVp1_30**
RFA (r) site, prescription dose 27.5Gy	**-**	**CTVr2_27.5**	**PTVr2_27.5**
TACE (t) site, prescription dose 27.5Gy	**-**	**CTVt2_27.5**	**PTVt2_27.5**
Non-HCC vascular (v) thrombosis, prescription dose of 27.5Gy	**-**	**CTVv2_27.5**	**PTVv2_27.5**

6.4.5 Critical Normal Structures will be contoured. Structures must be labeled using the Standard Name via TRIAD or resubmission will be required.

Description	Standard Name
Liver	Liver
Liver minus GTV	Liver_nonGTV
Esophagus	Esophagus
Stomach	Stomach
Duodenum	Duodenum
Small bowel*	SmallBowel
Large bowel*	LargeBowel
SpinalCord*^	SpinalCord
SpinalCord PRV5mm*^	SpinalCord _05
R kidney	Kidney_R
L kidney	Kidney_L
Kidneys	Kidneys
Optional contours to be contoured if > 30 Gy is planned to include these organs include:	
Skin	External
Chest wall*[t]	ChestWall
Gall bladder	Gallbladder
Common bile duct	Commonbileduct
Heart	Heart
Inferior vena cava	IVC

* At minimum, these structures are required to be contoured at the level of the PTV and over any region received > 10 Gy.
^Spinal canal and spinal canal PRV may be contoured instead of spinal cord and spinal cord PRV.
[t]As per lung SBRT RTOG atlas, the chest wall can be autosegmented from the ipsilateral lung with a 2-cm expansion in the lateral, anterior, and posterior directions. Anteriorly and medially, it ends at the edge of the sternum. Posteriorly and medially, it stops at the edge of the vertebral body with inclusion of the spinal nerve root exit site (Kong 2012).

An upper abdominal/liver atlas and lung OAR atlas (RTOG 1106), posted on https://www.nrgoncology.org/ciro-gastrointestinal, may be used as a guide for contouring. For duodenum contouring, the first and second portions must be contoured for all cases and the third and fourth portions should also be contoured if those portions receive > 10 Gy.

6.4.6 Heterogeneity Corrections: All dose distributions, photon and proton, shall include corrections for tissue heterogeneities. Arterial vascular contrast from the planning dataset is recommended to be converted to water equivalent density if used for planning. Planning datasets without intravenous contrast may be used for planning (and are required for protons).

6.4.7 Goals of planning are to maximize dose to the target volumes, while maintaining all normal tissue constraints (as defined in Section 6.5). **Reducing the maximal dose to all luminal gastrointestinal normal tissues should be a planning priority to reduce the risk of gastrointestinal toxicity.** Conformality of the prescription dose and the 30 Gy isodose are other goals.

6.5 Critical Structures Maximal Doses (27Oct2017)

Dose values in this section should be read as physical dose for photons, or RBE-weighted dose for protons, in 5 fractions (assuming RBE = 1.1).

6.5.1	Esophagus max (to 0.5 cc):	32 Gy
6.5.2	Stomach max (to 0.5 cc):	30 Gy
6.5.3	Duodenum max (to 0.5 cc):	30 Gy
6.5.4	Small bowel max (to 0.5 cc):	30 Gy
6.5.5	Large bowel max (to 0.5 cc):	32 Gy
6.5.6	Cord + 5 mm max (0.5cc):	25 Gy
6.5.7	Kidneys:	
	Bilateral mean dose < 10 Gy	
	-OR- If there is one kidney mean dose > 10Gy, remaining (or only) kidney V10Gy < 10%	

6.5.8 The following organ dose constraints are guidelines, not mandatory:

Stomach (to 5 cc):	< 25 Gy
Duodenum (to 5 cc):	< 25 Gy
Small bowel (to 5 cc):	< 25 Gy
Liver minus all GTVs:	> 700cc and V10Gy < 70%
Heart max (30cc):	< 30 Gy
Great vessel max (0.5 cc):	< 60 Gy
Skin (external) max (0.5 cc):	< 32 Gy
Chest wall max (0.5 cc):	< 50 Gy
Gallbladder max (0.5 cc):	< 55 Gy
Common bile duct max (0.5 cc)	< 50 Gy (even though the bile duct is not always well visualized, it is always within the portal region and may be within high dose volumes for central targets, so efforts to reduce hot spots in this region are warranted)

6.6 Targets and Critical Structures (27Oct2017)

Note: All required structures must be labeled for digital RT data submission as listed in the table. Resubmission of data may be required if labeling of structures does not conform to the standard dicom name listed.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD:

Standard Name	***Description***
GTVp(1,2,3,…)	All Parenchymal HCC
GTVv(1,2,3,…)	Vascular HCC thrombi or invasion
CTVp(1,2,3,…)	All Parenchymal HCC with no expansion of the GTV except where permitted in the protocol
CTVv(1,2,3,…)	Vascular HCC thrombi or invasion and may include expansion of the GTV
PTVp(1,2,3,…)_dose	All Parenchymal HCC with no more than a 20mm expansion of the CTVp. The dose that the PTV is treated to should be annotated, eg PTVp1_5000
PTVv(1,2,3,…)_dose	Vascular HCC thrombi or invasion with no more than a 20 mm expansion of the CTVv. The dose that the PTV is treated to should be annotated, eg. PTVv1_2750.
Liver	Liver*

Liver_nonGTV	Liver minus GTV*
Esophagus	Esophagus
Stomach	Stomach
Duodenum	Duodenum
SmallBowel	Small Bowel
LargeBowel	Large Bowel
SpinalCord	Spinal Cord
SpinalCord_05	Spinal Cord PRV
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Left and Right Kidney
External	Outer patient contour
GallBladder	Gall Bladder - optional
CommonBileDuct	Common Bile Duct – optional
Heart	Heart – optional
IVC	Inferior vena Cava –optional

* In addition to excluding GTV from liver volume to calculate the "liver minus GTV" volume, the following non-functional regions should be excluded from the 'liver' region of interest, when 1) the volume can be confidently identified and contoured; and 2) volume is > 2cm diameter.
    1) Hepatic cysts
    2) RFA cavities

    Note that the liver and exclusion structures should all be defined in the same image set when creating the liver minus GTV volume (e.g. subtract the GTV from the liver on the image set used for dose calculation. Do not contour and subtract the GTV on all phases of a 4DCT from the liver). The liver and GTV contours should be based on a breath hold CT, even if the dose calculation is done based on an average CT, as per section 6.3.2.

6.7 Documentation Requirements (8/26/14)

6.7.1 Quality Assurance Documentation

In patients randomized to the SBRT arm who do not receive radiation, the intended and/or best treatment plan should be submitted with an explanation for why the patient did not start radiation therapy.

For each institution, the full 3D dosimetry plans for the first three registered for this study and randomized to the SBRT arm will be reviewed in a pre-treatment review, PRIOR TO DELIVERY of radiation treatment. If these plans are within protocol compliance, then subsequent review of cases will be done in a timely review. Timely submission of all radiation plans is required for every patient treated on this study. The definition of timely submission for the patients requiring timely review is within 5 days of completion of radiation therapy.

Liver protocol CT scan and/or MR showing the extent of the tumor with contrast is required to be submitted. If multiple phases of CT and/or MR imaging, and/or if diagnostic CTs or MR imaging, are helpful for target delineation, multiple phase imaging datasets should be submitted. A maximum of three datasets per patient is to be submitted. These datasets should be submitted, registered as they were used for target delineation, which should be with the best fit liver-to-liver image registration, focusing on the region of the PTVs if deformation or rotation occurs between scans.

6.7.2 Treatment Interruptions

Treatment interruptions should be clearly documented in the patient's treatment record. Total treatment time is recommended to be 10 days, with allowable total duration between 5 days and 15 days (see Section 6.8.1).

6.7.3 Diagnostic CT/MR Submission Prior to Randomization

The baseline diagnostic CT or MR or a planning CT must be uploaded via TRIAD. The liver volume and the HCC and/or vascular thrombosis should be contoured in a radiation planning system or segmentation system prior to submission.

6.7.4 IGRT

For each IGRT technology, in addition to each "as if patient" dataset where imaging and offsets are submitted for 2 sequential fractions, the images and offsets for all days for the first two actual patients treated on study should be archived at the site in the event the data would be requested for review by the PI for future analysis..

For all subsequent patients, the IGRT images in treatment position for every fraction (and a table of subsequent 'shifts') are required to be archived at the site for possible subsequent future evaluation.

6.8 Compliance Criteria

The review process for this protocol is aimed at assuring correct contouring of target and critical structures, as well as appropriate planning. These reviews should avoid violations and deviations for this protocol. Each treatment shall be judged according to the protocol guidelines, with variations and deviations defined below:

6.8.1 Total Treatment Duration

Per protocol: All treatment falls within 15 calendar days
Variation Acceptable: All treatments fall within 16 to 21 calendar days
Deviation Unacceptable: All treatments that take 22 or more calendar days to complete

6.8.2 GTV Compliance

Per protocol: no edits required
Variation acceptable: Variations in GTV or CTV other than deviation unacceptable
Deviation unacceptable: Definite HCC or enhancing thrombosis not contoured within GTV

6.8.3 PTV Compliance

PTV Contouring

Per protocol: PTV > 4 mm and < 20 mm
Variation acceptable: PTV 3-4 mm or 20-25 mm
Deviation unacceptable PTV < 3 mm or > 25 mm

PTV Dosimetry

Target coverage for each PTV should be considered on its own.
If there are multiple tumors, the primary (dominant) PTV should be labeled #1.
The intent is for prescription dose to cover 95% of each PTV. If PTVs are not treated as per guidelines, this is a deviation unacceptable. The PTV should be treated to as high a dose as possible, respecting normal tissue constraints (as per Section 6.1.5), as a dose response has been observed. Modifying required PTVs due to close proximity of adjacent OARs is not permitted.

The following table describes variations and deviations in the prescription dose (dose covering 95% of the PTV). **Treating "per protocol" should always be the planning intent.**

Dose to 95% PTV	PTVs around GTVs *	PTVs around non-GTV CTVs*
per protocol	prescription dose +/- 5%	prescription dose +/- 5%
variation acceptable	90-95% or 105-110% of prescription dose, and ≥ 25 Gy	85-95% or 105-115% of prescription dose and ≥ 25 Gy
deviation unacceptable	<90% or >110% of prescription dose, or < 25 Gy	<85% or >115% of prescription dose, or <25Gy
Overall plan deviation unacceptable	< 25 Gy	

Dose values in this section should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1). *Note that lower doses than the dose-allocation schedule are acceptable if they are required due to adjacent GI luminal structures that may limit the deliverable dose.

6.8.4 Compliance for Critical Structures (organs at risk, OARs)

If non-hepatic OARs limit the prescription dose, the highest dose (from the 6 prescription doses listed in Section 6.1.5) should be used, while maintaining OAR dose constraints.

Non-liver OARs	per protocol	variation acceptable	deviation unacceptable
Esophagus max (to 0.5 cc):	32 Gy	> 32 but ≤34 Gy	> 34 Gy
Stomach max (to 0.5 cc):	30 Gy	>30 but ≤32 Gy	> 32 Gy
Duodenum max (to 0.5 cc):	30 Gy	>30 but ≤32 Gy	> 32 Gy
Small bowel max (to 0.5 cc):	30 Gy	>30 but ≤32 Gy	> 32 Gy
Large bowel max (to 0.5 cc):	32 Gy	>32 but ≤34 Gy	> 34 Gy
SpinalCord_05 + 5 mm max (0.5cc):	25 Gy	>25 but ≤28 Gy	> 28 Gy
Kidneys: Bilateral mean dose	≤10 Gy	>10 but ≤12 Gy	> 12 Gy
Dose values in these tables should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1).			

Prescription dose	Liver (minus GTV) mean dose		
	per protocol	variation acceptable	deviation unacceptable
50 Gy	≤13 Gy	13-13.2 Gy	> 13.2 Gy
45 Gy	≤15 Gy	15-15.2 Gy	> 15.2 Gy
40 Gy	≤15 Gy	15-15.2 Gy	> 15.2 Gy
35 Gy	≤15.5 Gy	15.5-15.7 Gy	> 15.7 Gy
30 Gy	≤16 Gy	16-16.2 Gy	> 16.2 Gy
27.5 Gy	≤17 Gy	17-17.2 Gy	> 17.2 Gy
Dose values in these tables should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1).			

6.9 Radiation Therapy and Imaging Quality Assurance Reviews (27Oct2017)

6.9.1 Rapid and Timely Review of RT Plans

For each technique (non-IMRT, non-proton SBRT, IMRT and/or protons), the first three patients to be treated at the site on this protocol will have a pre-treatment review of their plans, i.e. the individual plan needs to be approved PRIOR to delivering any protocol treatment for patient or subsequent patients. After pre-treatment review by the PI, suggestions regarding protocol compliance will be forwarded to the participating institution. Pre-treatment review of all plans PRIOR to treatment delivery will continue until at least 3 plans have been submitted without deviations. If any protocol deviations are found in the first 3 plans, pre-treatment review will continue until at least at least three sequential plans have been approved without deviations. All radiation plans need to be submitted in a timely manner– ideally at least 5 days prior to planned start of therapy for pre-treatment reviews and within 1 week (5 working days) post RT completion for timely reviews. The remaining reviews will be completed remotely and be ongoing. The final cases will be reviewed within 3 months after the study has reached the target accrual or as soon as IROC Philadelphia RT has received complete data for all cases enrolled, whichever comes first. The scoring mechanism is: Per Protocol, Acceptable Variation and Deviation Unacceptable.

All additional QA data (including actual treatment details) is to be submitted within 1 week of RT end.

6.9.2 Planned Interim Analyses of Quality Assurance

After first 50 patients are enrolled and/or first 25 patients randomized to the SBRT arm (whichever comes first), the Radiation Oncology Chair and Co-Chairs, along with a delegated team from NRG Oncology, will summarize all QA results. All submitted imaging datasets for both arms of the study will be reviewed as will imaging, contouring and HCC:liver strata determination. Following this analysis, modifications to education material and/or the protocol to help prevent violations and deviation for future patients, may be recommended.

Secondary reviews will occur after the first 100 and 200 patients are enrolled, again with a plan to improve education material and/or the study if needed, with individual feedback to participating institutions.

6.9.3 Pre-Randomization Imaging Submission for All Patients (including non-radiation patients)

For all patients randomized, submission of IV contrast CT or MR with contouring of the HCC, (including vascular thrombi) and calculation of the HCC GTV/liver volume stratification factor is required. This imaging may be done in radiation planning CT and/or may be done on diagnostic CT or MR imported to a radiation planning system or any platform that allows organ segmentation and data transfer. The first 3 cases per institution from patients randomized to the non-RT arm will be reviewed (timely) by the PI or designee. Any differences in the segmentation of tumor or liver or in the tumor:liver volume calculation will be recorded. Feedback to each institution will follow in a timely manner (regarding imaging quality or contouring).

Rationale for use of the ratio of the GTV to liver volume as a stratification factor is that the ratio of HCC to liver volume is a known prognostic factor for HCC. Prognosis is best in patients with a small volume of HCC, and toxicity is increased in those with a smaller volume of liver. The GTV/liver volume takes into account both these factors. Furthermore, in the radiation arm, the radiation dose is expected to be associated with local control probability. Based on the PMH SBRT experience (Bujold 2012), dose is correlated with GTV/liver volume. Stratification categories were based on values from a sample of patients treated at PMH. Central review of assessment of the calculation of this stratification factor will help ensure the quality of calculation of GTV:liver, and will provide insight regarding the quality of imaging and selection of tumors for this study, even in the non-SBRT arm patients. Feedback to centers may help improve quality or patient selection for future cases.

6.10 Radiation Therapy Adverse Events

The criteria used for the grading of toxicities encountered in this study are Common Toxicity Criteria (CTC) version 4.0.

Very likely (80-90%)

- Fatigue (which generally goes away after the radiation therapy is completed)
- Skin irritation, redness, itchiness, discomfort
- Temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

Less likely (30%)

- Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal track irradiated
- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (<10% permanent changes)
- Chest wall pain, rib fracture (< 10%)

Less likely, but serious (<20%)

- Radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver.
- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

6.11 Radiation Therapy Adverse Event Reporting

See Section 7.4 for details on adverse event reporting.

6.12 Radiation Therapy Toxicity Assessment During Therapy (27Oct2017)

Patients will be assessed at least once during radiation therapy for toxicity (as per Appendix I). Radiation therapy will continue as planned as long as there is no grade 3 or 4 toxicity, bilirubin is <3 mg/dL, Child score is Child Pugh ≤7 and the treating physician recommends continuation. Otherwise, a delay in radiation therapy should occur with possible continuation of radiation if it resolves as per Section 6.12.1.

If the patient discontinues radiation therapy prematurely, the patient may be considered for study sorafenib, if the Child score is Child Pugh ≤7 and the treating physician recommends protocol treatment continuation.

6.12.1 Radiation Modification Table

TOXICITY	MODIFICATION
Hematologic Toxicities	
grade 1 or 2	Continue radiation
grade 3	Hold radiation until ≤ grade 2, then continue
grade 4	Hold radiation 1 week and until ≤ grade 2, then continue
Gastrointestinal Toxicities	
grade 1 or 2	Continue radiation
grade ≥ 3 diarrhea	Hold radiation until improves to ≤ grade 2, then resume
grade 1 or 2 nausea or vomiting	Initiate anti-emetics prior to radiation and as needed and continue radiation
grade 3 nausea or vomiting	Hold radiation until improves to ≤ grade 2, then resume with anti-emetics prior to radiation and as needed
Hepatic Dysfunction	
bilirubin 1.3-3.0 mg/dL	Continue radiation
bilirubin > 3.0 mg/dL	Hold radiation until improves to ≤ 3.0, then resume
grade 1 or 2 AST or ALT	Continue radiation
grade 3, < 10x ULN AST or ALT	Continue radiation
grade 3, > 10x ULN AST or ALT	Hold radiation until improves to ≤ grade 2, then resume
grade 4 AST and ALT	Hold radiation for one week and until improves to ≤ grade 2, then resume
Child-Pugh score > 7	Hold radiation until improves to Child-Pugh score ≤ 7
Other non-hematologic Toxicities	
grade 1, 2	Continue radiation

grade 3	Hold radiation until improves to ≤ grade 2, then resume
grade 4	Discontinue radiation

7.0 DRUG THERAPY (27OCT2017)

Protocol treatment is encouraged to begin as soon as possible after study entry. Protocol treatment must begin within 21 days after study entry, unless extra time is needed for fiducial marker insertion, but not to exceed 28 days.

7.1 Treatment (14-SEP-2020)

Although sorafenib dosing is recommended as per the following sections, if clinically indicated, dose modifications (reductions or alternative dosing, never more than 400 mg po bid) are permitted, based on the investigator's discretion taking into account the patient's entire clinical picture. This may occasionally include starting patients at half dose sorafenib, even in the control arm.

7.1.1 Dose Definition

ARM I *(Control Arm)*	Day 1-Start Sorafenib 400mg BID daily (Dose level 0). Each cycle=28 continuous days.
ARM 2 *(Experimental Arm)*	Sorafenib to start Day 1-5 post SBRT completion at 200mg BID (level -1). Each cycle=28 days. Sorafenib will be increased to 400mg BID during cycle #2 if clinically appropriate, as per Section 7.1.1.

For arm 2, the sorafenib may be escalated to full dose (400mg BID) during cycle #2 if there is no dose limiting toxicity requiring dose reduction as per Section 7.2.3, the Child score is Child Pugh ≤7 and the treating physician recommends escalation. If escalation is not recommended at cycle #2 for arm 2, escalation should be reconsidered at cycle #3 and each subsequent cycle if escalation is still not recommended. For patients who discontinue radiation therapy prematurely, they should be considered for sorafenib, as per arm 2, according to the above guidelines.

7.1.2 Technique of Administration: Oral

Availability/Supply: Commercially available. Sites must refer to the package insert for detailed pharmacologic and safety information. Please see Sections 7.1-7.2 for administration instructions. Please refer to the current sorafenib package insert and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage

- Non-Canadian International Institutions: Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.1.3 Duration of Treatment

Arm 1 (Control Arm): Sorafenib Alone
Sorafenib will continue until progression, unacceptable toxicity or for a maximum of 5 years.
Arm 2 (Experimental Arm): SBRT Followed by Sorafenib
Sorafenib will continue until progression, unacceptable toxicity or for a maximum of 5 years.

All sorafenib doses that are held/missed should be documented. Patients who have missed a sorafenib dose should take the next scheduled dose. There should not be any make-up of missed doses. A drug diary (to be maintained at the site) is recommended to be used and reviewed at each follow-up visit.

Sorafenib dose de-escalation should occur for toxicity, as outlined in Section 7.2. Patients will be considered off protocol treatment if sorafenib is held for 3 weeks.

Although sorafenib dosing is recommended as per the following sections, if clinically indicated, dose modifications (reductions or alternative dosing, never more than 400 mg po bid) are permitted, based on the investigator's discretion taking into account the patient's entire clinical picture. This may occasionally include starting patients at half dose sorafenib, even in the control arm.

7.1.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Sorafenib (BAY 43-9006; Nexavar, NSC 724772)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2571 patients.* Below is the CAEPR for Sorafenib (BAY 43-9006; Nexavar).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.10, June 24, 2020[1]

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
CARDIAC DISORDERS			
	Chest pain - cardiac		
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 3)***
	Ascites		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Gastrointestinal hemorrhage[2]		***Gastrointestinal hemorrhage[2] (Gr 3)***
		Gastrointestinal perforation[3]	

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications - Other, specify (wound healing complication)	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		***Activated partial thromboplastin time prolonged (Gr 2)***
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
Alkaline phosphatase increased			***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
Creatinine increased			***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	GGT increased		
INR increased			***INR increased (Gr 3)***
	Investigations - Other (Bicarbonate-serum low)		
Lipase increased			***Lipase increased (Gr 3)***
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 3)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
Serum amylase increased			***Serum amylase increased (Gr 3)***
		Thyroid stimulating hormone increased	
Weight loss			***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 3)***
	Hypernatremia		
Hypoalbuminemia			***Hypoalbuminemia (Gr 3)***
Hypocalcemia			***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 3)***
Hyponatremia			***Hyponatremia (Gr 3)***
Hypophosphatemia			***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
	Back pain		***Back pain (Gr 3)***
	Bone pain		
	Muscle cramp		
	Myalgia		
	Pain in extremity		***Pain in extremity (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Treatment related secondary malignancy		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Respiratory hemorrhage[5]		
	Voice alteration		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage may include Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation may include Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5]Respiratory hemorrhage may include bronchopulmonary hemorrhage, epistaxis, laryngeal hemorrhage, mediastinal hemorrhage, pharyngeal hemorrhage, and pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[6]Febrile neutropenia is seen mostly in combination with other agents.

Adverse events reported on sorafenib (BAY 43-9006; Nexavar) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that sorafenib (BAY 43-9006, Nexavar) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (Thrombotic microangiopathy (e.g., TTP or HUS)); Febrile neutropenia[6]
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Palpitations; Pericardial effusion; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Adrenal insufficiency; Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (color vision deficits); Eye disorders - Other (light to dark adaptation); Eye disorders - Other (retinal vein occlusion, bilat); Eye disorders - Other (retinal hemorrhage); Eye disorders - Other (visual field distortion); Flashing lights; Keratitis; Photophobia; Retinal detachment
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fistula; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophagitis; Flatulence; Gastric ulcer; Gastritis;

Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (small bowel NOS fistula); Gastrointestinal fistula; Hemorrhoids; Ileal fistula; Ileus; Oral pain; Pancreatitis; Proctitis; Rectal fistula; Rectal mucositis; Rectal obstruction; Rectal pain; Small intestinal obstruction; Stomach pain; Visceral arterial ischemia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Facial pain; Flu like symptoms; Localized edema; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic hemorrhage; Hepatobiliary disorders - Other (biliary obstruction secondary to multiple biliary stones)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Cytokine release syndrome; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Fall; Fracture; Hip fracture; Vascular access complication; Wound dehiscence
INVESTIGATIONS - CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; Fibrinogen decreased; Investigations - Other (blood urea nitrogen high)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hyperuricemia; Hypomagnesemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (cramping); Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Hydrocephalus; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Muscle weakness left-sided; Muscle weakness right-sided; Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Libido decreased; Personality change; Psychosis
RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (focal segmental glomerulosclerosis); Renal and urinary disorders - Other (right ureter rupture); Renal calculi; Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urine discoloration
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Gynecomastia; Hematosalpinx; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal fistula; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Bronchospasm; Hiccups; Hoarseness; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (nasal septal perforation); Tracheal mucositis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Hyperhidrosis; Nail loss; Pain of skin; Purpura; Rash acneiform; Scalp pain; Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratocanthomas type); Skin hyperpigmentation; Skin hypopigmentation; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypotension; Phlebitis; Vascular disorders - Other (ruptured aortic aneurysm); Vasculitis

Note: Sorafenib (BAY 43-9006; Nexavar) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.5 Potential Drug Interactions

- *CYP3A4 Inducers*

Chronic concomitant administration of rifampin with a single dose of sorafenib resulted in a 24% decrease in the combined AUC of sorafenib and its active primary metabolite when rifampin was co-administered with sorafenib. The clinical significance of this overall decrease in drug exposure is unknown. **Other inducers of CYP3A4 activity (eg, hypericum perforatum [also known as St. John's wort], phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase the metabolism of sorafenib and decrease its exposure.**

- *CYP2C9 Substrates*
  The possible effect of sorafenib on warfarin, a CYP2C9 substrate, was assessed in sorafenib-treated patients compared to placebo-treated patients. The concomitant treatment with sorafenib and warfarin did not result in changes in mean PT-INR compared to placebo. However, patients taking warfarin should have their INR checked regularly (see Product Monograph: WARNINGS AND PRECAUTIONS and PART II: DETAILED PHARMACOLOGY).
- *CYP Isoform-selective Substrates*
  Concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, following 4 weeks of sorafenib administration did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes are unlikely.
- *UGT1A9 Inhibitors*
  An in vitro study has revealed a number of drugs affected UGT1A9-mediated sorafenib glucuronidation with an IC50 value below 100 μM. They were atorvastatin (IC50 = 67 μM), ketoconazole (87 μM), mefenamic acid (28 μM), erlotinib (69 μM), and niflumic acid (1.2 μM). T
  he clinical relevance of these drug interactions has not been tested.
- *Combination with Other Antineoplastic Agents*
  Sorafenib is approved only as monotherapy in the treatment of RCC and HCC (see Product Monograph: INDICATIONS AND CLINICAL USE). In clinical studies, sorafenib has been administered together with a variety of other antineoplastic agents at their commonly-used dosing regimens, including gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see Product Monograph: WARNINGS AND PRECAUTIONS). A clinical study has revealed that administration of sorafenib with a 3-day break in dosing around administration of docetaxel resulted in a 36-80% increase in docetaxel AUC and a 16-32% increase in docetaxel Cmax (see Product Monograph: WARNINGS AND PRECAUTIONS).

7.1.6 Storage

Store at controlled room temperature (15ºC – 25ºC). Storage conditions should not exceed 25ºC.

Stability

The stability profile of the solid drug is excellent. In solid form, sorafenib is stable at room temperature for up to 24 months, and it is insensitive to light. The expiration date should be readily available on the label of commercially supplied sorafenib.

7.2 Dose Modifications (27Oct2017)

NOTE: The dose modifications are recommended modifications. The final dosing should be based on the investigator's discretion taking into account the patient's entire clinical picture. The goal is that the patient will stay on the drug for as long as possible (even if reduced dose) if there is clinical benefit, no progression and the patient is tolerating sorafenib.

Protocol treatment may be dose modified based on criteria outlined in the dose modification table (Section 7.2.3). For both arms, after each cycle (28 days), assessment for toxicity will be made. The sorafenib will be continued at the present dose (or escalated to full dose during cycle #2 or subsequent cycles for arm 2) if there is no dose limiting toxicity requiring dose reduction as per Section 7.2.3, the Child score is Child Pugh ≤7 and the treating physician recommends continuation. If the Child Pugh score is B7, and the patient is otherwise suitable for sorafenib, sorafenib should be delivered at half dose. If at subsequent evaluations demonstrate recovery to CP <= 6 and no other competing toxicity then Sorafenib can be re-escalated to full dose.

For both arms, it is not the intention to take patients off sorafenib early for minor changes in liver function.

7.2.1 Once reduced for toxicity, Sorafenib may or may not be re-escalated per the investigator's discretion. If dose reductions beyond dose level -2 are required or drug is held for more than 3 weeks, all protocol therapy will be discontinued.

If more than one of these apply, use the most stringent (i.e., the greatest dose reduction).

7.2.2 Dose Reduction Table

Dose level 0 (starting dose, 800 mg po)	2 x 200 mg po every 12 hours
Dose level -1 (400 mg po)	1 x 200 mg po every 12 hours
Dose level -2 (200 mg po)	1 x 200 mg po daily

7.2.3 Dose Modification Table

NOTE: The dose modifications are recommended as minimum required modifications. The final dosing should be based on the investigator's discretion taking into account the patient's entire clinical picture. The goal is that the patient will stay on the drug for as long as possible (even if reduced dose) if there is clinical benefit, no progression and the patient is tolerating sorafenib.

TOXICITY	MODIFICATION
Hematologic Toxicities	
grade 1 or 2	Continue sorafenib
grade 3	Continue sorafenib at one reduced dose level
grade 4 or neutropenic fever	Interrupt sorafenib until ≤ grade 2, then continue at one reduced dose level
Gastrointestinal Toxicities	
grade 1 or 2	Continue sorafenib
grade ≥ 3 diarrhea	Interrupt sorafenib until improves to ≤ grade 2, then resume sorafenib at one reduced dose level
grade ≥ 3 nausea or vomiting despite antiemetics	Interrupt sorafenib until improves to ≤ grade 2, then resume sorafenib at one reduced dose level
Hepatic Dysfunction	
bilirubin 1.3-3.0	Continue sorafenib
bilirubin > 3.0	Discontinue sorafenib
Child-Pugh score > 7	Interrupt sorafenib until improved to Child-Pugh score 7 or less. Sorafenib is to be re-started at half dose, if Child-Pugh score is B7, and it can be re-escalated to full dose if Child-Pugh score returns to A.

Skin Toxicity: Rash (Maculo-Papular) or Hand-Foot Skin Reaction (HFSR; Palmar-Plantar Erythrodysesthesia)	
grade 1	Continue sorafenib
grade 2, 1st appearance	Interrupt sorafenib until improves to ≤ grade 1, then resume sorafenib at the previous dose level
grade 2, 2nd or 3rd appearance	Interrupt sorafenib until improves to ≤ grade 1, then resume sorafenib at one reduced dose level
grade 2, 4th appearance	Discontinue sorafenib therapy
grade 3, 1st or 2nd appearance	Interrupt sorafenib until toxicity improves to ≤ grade 1, then resume sorafenib at one reduced dose level
grade 3, 3rd appearance	Discontinue sorafenib therapy
Following a full cycle (one month) of reduced dose sorafenib with no rash or HFSR of ≥ grade 1 severity, the dose of sorafenib may be re-escalated to the previous dose level. (Note: Re-escalation is allowed only in the case of skin toxicity.)	
Hypertension	
hypertension controlled with medication (to <140/90)	Continue sorafenib
hypertension >140/90 and ≤160/100	Continue sorafenib Consider adding or adjusting anti-hypertensive medications
persistent (>160/100) or symptomatic hypertension	Interrupt sorafenib Resume when blood pressure improves to <160/100 If sorafenib is interrupted for ≥3 weeks, discontinue sorafenib
grade 4	Discontinue sorafenib therapy
Other non-Hematologic Toxicities	
grade 1, 2	Continue sorafenib
grade 3	Interrupt sorafenib until toxicity resolves to ≤ grade 1, then reduce by one dose level
grade 4	Discontinue sorafenib therapy

7.2.4 Toxicity Management

Management of Skin Toxicity: At first occurrence of HFSR, independent of grade, supportive measures such as topical emollients, low potency steroids, or urea-containing cream should be administered.

7.3 Modality Review (8/26/14)

The Medical Oncology Co-Chairs, Andrew Zhu, MD and/or Jennifer Knox, MD, will perform a Systemic Therapy Assurance Review of patients who receive protocol-specified systemic therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of systemic therapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

This Systemic Therapy Assurance Review will be performed on an ongoing basis (for example, the first review after NRG Oncology receives complete data for 20 cases and the next review after NRG Oncology receives complete data for 20 more cases). The final cases will be reviewed

within 3 months after this study has reached the target accrual or as soon as NRG Oncology receives complete data for all cases, whichever occurs first.

7.4 Adverse Events (13-MAY-2019)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

7.4.1 Adverse Events (AEs)

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

7.4.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.5 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.5. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

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

7.4.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

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

7.5 CTEP-AERS Expedited Reporting Requirements (27Oct2017)

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

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

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

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Operations Office at 215-574-3191, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Contact NRG Oncology at 1-215-574-3191 for details to submit source documentation.
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Commercially Available Agent [1, 2]

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

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of commercially available agent and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing Commercially Available Agent:
Not applicable

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

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

9.1.2 Antiemetics (e.g. dopamine (D2) receptor antagonist or 5HT3 antagonists) should be considered to be used prior to each fraction of SBRT to prevent nausea if the stomach is anticipated to receive any radiation. They may also be used for symptomatic nausea or vomiting.

9.1.3 Antidiarrheals may be used to treat therapy induced diarrhea.

9.1.4 H2 blockers or proton pump inhibitors are strongly recommended if 20 Gy or more is delivered to the luminal gastrointestinal tract or at the treating physicians discretion. They should start before completion of SBRT and continue for at least 6 months.

9.1.5 Analgesics may be used to treat tumor or therapy induced pain. NSAIDS are recommended to be avoided to reduce luminal GI irritation.

9.1.6 In the occurrence of liver toxicity (including classic RILD, non-classic RILD or any CTCAE 4.0 grade 4 toxicity or any sorafenib associated liver toxicity, occurring in the absence of HCC progression within 12 weeks of completion of radiation therapy), best supportive care and possible diuretics are recommended. Steroids may be used, and a referral to a hepatologist is recommended.

9.1.7 Topical creams, emollients, balms, low potency steroids or urea containing creams are recommended for discomfort due to hand foot syndrome.

9.1.8 Anti-hypertensives should be used for sorafenib-induced increase in blood pressure. Calcium channel blockers are recommended.

9.2 Non-permitted Supportive Therapy (27OCT2017)

9.2.1 Anticoagulants are not recommended to be used to treat HCC related vascular thrombosis. They may be used for bland thrombosis or pulmonary emboli.

10.0 TISSUE/SPECIMEN SUBMISSION (27OCT2017)

Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking and translational research (recommended).

10.2 Specimen Collection for Tissue Banking and Translational Research (27Oct2017)

For patients who have consented to participate in the tissue/blood component of the study. The following must be provided in order for the case to be evaluable for the Biospecimen Bank – San Francisco.

10.2.1 One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block); it does not have to be the diagnostic slide itself).

10.2.2 A corresponding paraffin-embedded tissue block of the tumor (preferred, the block must match the H&E being submitted) or 10 unstained slides (5 micron cut onto positive charged slides) of tumor tissue. Block or slides must be clearly labeled with the pathology identification number and block number that corresponds to the Pathology Report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.3 A Pathology Report documenting that the submitted block or slides contains tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank – San Francisco; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

For specimen collection: See Appendix IX for the specimen collection kits and instructions. The following materials must be provided to the NRG Oncology Biospecimen Bank – San Francisco: An ST documenting the date of collection of the biospecimen; the NRG Oncology protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.2.5 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the ST Form the storage conditions used and time stored.

10.2.6 Specimen Collection Summary

Specimens for Tissue Banking/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide	Slide shipped ambient to NRGBB-SF
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment	Pre-treatment	Paraffin-embedded tissue block. If a block is not available then 10 unstained slides (5 micron cut onto positively charged slides)	Block or slides shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-treatment (baseline) 1 and 3 months from study entry	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Serum sent frozen on dry ice via overnight carrier to NRGBB-SF in batch shipments
PLASMA: 5-10 mL of	Pre-treatment	Frozen plasma	Plasma sent frozen on

anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	(baseline) 1 and 3 months from study entry At the time of progression and/or grade 4 liver toxicity (within 4 weeks)	samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	dry ice via overnight carrier to NRGBB-SF in batch shipments
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment Note: If site missed this collection time point they may collect whole blood for DNA at a later time point instead but must note this on the ST Form.	Frozen whole blood samples containing 1-2 mL per aliquot in 2 mL cryovials (three)	Whole blood sent frozen on dry ice via overnight carrier to NRGBB-SF in batch shipments

10.2.7 Submit materials for Tissue Banking and Translational Research as follows:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco – Box 1800

2340 Sutter Street, Room S341
San Francisco, CA 94143

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.3 Confidentiality/Storage (13-MAY-2019)

10.3.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.3.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

Patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life (QOL) assessment. If the patient consents to participate in the QOL component of the study, sites are required to administer the baseline QOL and functional assessments prior to the start of protocol treatment.

11.1 Study Parameters

See Appendix I. Timing of all follow-up imaging and other assessments is from registration for both arms of the study.

11.2 Evaluation During Treatment

11.2.1 Once PD has occurred, patients need to follow the study on-treatment calendar. Documentation of all subsequent therapies should occur. The follow-up schedule post-treatment is outlined in Appendix I.

11.3 Measurement of Response (25-MAR-2020**)**

11.3.1 **See Appendix I** (Study Parameter Table). Note, response in the irradiated volume is challenging to assess before 3 months post radiation therapy due to radiation change in the surrounding liver. Even at 3 months, changes in the surrounding liver around the HCC may represent radiation treatment change, rather than tumor progression. Thus, review of images by experienced radiologists is required, as is importance of relaying radiation information to the radiologists, to avoid inaccurate labeling of progression when liver changes are due to radiation effect on the liver.

It is strongly recommended to use the same method of assessment (i.e. comparable scanners and imaging techniques) from one scan to the subsequent scans. For example, multi-phasic CT scans should be used with the same slice thickness for each follow-up scan. It would not be appropriate to compare a pre-treatment non-contrast liver MRI on a 0.5T scanner with 0.5 cm slice thickness to a post-treatment gadolinium enhanced MRI on a 3T scanner with 0.2 cm slice thickness (nor vice versa). If a patient develops a contraindication to CT IV contrast, then contrast MR may be used to follow the patient. If a patient develops a contraindication to MR IV contrast, then non-contrast MR and/or US is recommended for follow-up. Imaging details are outlined in Appendix V.

11.3.2 Response will be evaluated in this study using the international criteria proposed in the Reviewed Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 (Eur J Cancer: 2009: 45:228-247). Response will be assessed locally, with no planned central review.

Overall response will be measured (based on assessment of target lesions), as well as irradiated lesion response (defined as response of the target measurable disease included in the radiation volume). Response measurements, including response assessment of tumor thrombosis as per Section 11.3.3, will take place every 3 months, according to the schedule in Appendix I.

Measurable disease is defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded), e.g. liver lesions ≥ 10mm by CT scan with slice thickness no greater than 5 mm, nodes ≥ 15mm in short axis by CT. All tumor measurements should be recorded in millimeters.

Non-measurable disease is defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathologic lymph node ≥ 10mm and ≤ 15 mm) and any vascular thrombosis. Other non-measureable disease includes ascites, pleural effusions.

- *Response criteria: Evaluation of target lesions*

  Target lesions: All measureable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (longest diameters) and their suitability for accurate repeated measurements. Vascular thrombi will not be included as target lesions.

  Target irradiated lesions (for SBRT arm only): All measureable lesions up to a maximum of two lesions in the liver, within the irradiated volume. Target lesions should be selected on the basis of their size (longest diameters) and their suitability for accurate repeated measurements. The sum of longest diameters (in any dimension) of target lesions will be used to characterize the objective tumor response. Vascular thrombi will not be included as target irradiated lesion,

unless vascular HCC is the only HCC present, in which case it can be used as the target lesion. Response for vascular thrombi will follow Section 11.3.3.

Complete response (CR): Disappearance of all measurable target lesions. Any pathological nodes (whether target or non-target) must have reduction in short axis to < 10mm.

Partial response (PR): At least 30% decrease in the sum of the longest diameters of the target lesions, taking as reference the baseline sum diameters.

Progressive disease (PD): At least 20% increase in sum of the longest diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. Unequivocal, unambiguous progression of non-measurable disease is included as PD. For vascular thrombosis (consistent with Section 11.3.3), this is defined as:

a) Unequivocal, unambiguous new enhancing tumor thrombosis or
b) Unequivocal, unambiguous increase in the volume of enhancing portion of thrombosis

Stable disease (SD): No change or small changes that do not meet the above criteria for PR or PD, taking as reference the smallest sum diameters while on study.

11.3.3 Vascular Thrombosis Response

There are no validated guidelines to monitor and report vascular thrombosis response. Consistent with RECIST1.1, thrombosis will be considered non-measurable disease. Response of vascular thrombosis will be recorded as a secondary endpoint in this study, using the following guidelines:

CR thrombosis: Complete resolution of thrombosis, with recanalization of vessel.

PR thrombosis: any of

a) Partial recanalization of thrombosis (if prior complete blockage)
b) Unequivocal reduction in the maximal girth of thrombosis
c) Unequivocal reduction in the volume, or elimination, of arterial enhancing portion of thrombosis

PD thrombosis: any unequivocal, unambiguous,

a) New enhancing tumor thrombosis
b) Increase in the volume of enhancing portion of thrombosis

Note that for “unequivocal progression” of thrombosis (non-measurable disease), the increase in overall tumor burden (enhancing thrombosis) must be comparable to the increase required for RECIST1.1 definition of PD of measurable disease (e.g. at least 73% increase in volume, which is similar to 20% increase in diameter, and at least a 5 mm absolute increase).

SD thrombosis: any of

a) No change or small changes that do not meet the above criteria for PR or PD, taking as reference the smallest sum diameters while on study.
b) Increase in the volume of non-enhancing thrombosis
c) New bland non-enhancing thrombosis

11.4 Criteria for Discontinuation of Protocol Treatment (8/26/14)

11.4.1 Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease, as defined in Section 11.3. Note that there are no accepted guidelines for assessing progression or response of vascular HCC to therapy. Thus, discontinuation of protocol treatment should only occur in reaction to changes in vascular thrombosis response if the progression is unequivocal and of substantial magnitude (estimated > 73% increase in volume of enhancing vascular HCC and > 5 mm absolute increase) and the investigator believes discontinuation is in the patient’s best interest. If there is any doubt about the ‘unequivocal’ nature of the vascular progression, patients should remain on therapy.

- Unacceptable adverse event(s), as defined in Section 6.0 and/or 7.0 and/or 13.5.4
- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Pregnancy
- Delay in protocol treatment > 3 weeks, as specified in Section 7.0.

Reasons for discontinuation from protocol treatment should be documented in the patient's medical record and case report Form (CRF).

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

11.4.3 Any salvage treatment will be recorded. If radiation therapy is offered for salvage post sorafenib in patients not randomized to SBRT, total dose, dose per fraction and overall time should be recorded and reported on the Salvage RT form. In this situation, radiation therapy is only recommended if the patient meets eligibility criteria similar to baseline eligibility of this study.

11.5 Health Related Quality of Life and Health Utility Assessments (27Oct2017)

11.5.1 Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)

FACT-Hep version 4 is a 45-item self-report instrument designed to measure health-related quality of life (HRQL) in patients with hepatobiliary cancers. The FACT-Hep consists of the 27-item FACT-General (FACT-G), which assesses generic QOL concerns, and the newly validated 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues. Patients are asked to score each item for the past week on a 4-point likert scale (from 0 "not at all" and 4 "very much"). The total FACT-Hep score is the sum of the four sub-scale scores and ranges from 0 to 108; it takes less than 15 minutes to complete and is translated in 45 languages. The FACT-Hep is validated and presents good internal consistency, test–retest reliability, and convergent and discriminate validity in patients with hepatobiliary cancer and HCC Heffernan 2002, Steel 2006, Wang 2007, Steel 2004). The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. Note: The FACT-Hep has been validly translated into many languages and will be available in languages beyond English on the RTOG 1112 page of the CTSU website. Patients eligible for QOL analyses need to provide informed consent, and translated FACT-Hep QOL questionnaires must be available in their primary language.

FACT-Hep QOL will be administered at baseline, 3 months, 6 months and 12 months post initiation of protocol therapy. Patients will be included in the QOL analyses only if they have provided both baseline and at least 1 subsequent measurement.

11.5.2 EuroQol (EQ-5D)

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

The EQ-5D will be administered at baseline, 3 months, 6 months and 12 months post initiation of protocol therapy. Patients will be included in the quality-adjusted survival analyses only if they have provided both baseline and at least 1 subsequent measurement.

11.5.3 Quality-Adjusted Survival

The EQ-5D will be used to assess quality-adjusted survival. Quality-adjusted survival is the weighted sum of different time in different health states added up to a total quality-adjusted

survival time [U=sum of quality (qi) of health states K times the duration (si) spent in each health state] (Glasziou 1990).

12.0 DATA COLLECTION

12.1 Data Quality Portal (23-SEP-2022)

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

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

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

12.2 Data Submission / Data Reporting (23-SEP-2022)

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

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or e-mail at ctsucontact@westat.com.

12.2.1 Summary of Data Submission

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

Folder	Form/Item
Registration via the OPEN System	• ***Subject Enrollment Form***
Enrollment **When pushed into RAVE there will be 5 forms representing registration**	• ***Demography Form*** • ***Step Information Form*** • ***Treatment Assignment Form*** • ***Eligibility Checklist Form***
Baseline folder	• ***Patient History Form (formerly known as the A5)*** • ***Work Up*** • ***Other Conditions*** • ***Lab Results*** • ***Pathology Report (Upload of report is required)*** • ***EQ-5D and FACT-HEP if consented for QOL*** • ***Digital Data (RT Plan)(Arm 2)*** • ***Pretreatment Scan (Arm 1)*** • ***Sorafenib Details (if received prior Sorafenib)***
Month 1 Visit-Arm 1	• ***Lab Results*** • ***Protocol Specific Adverse Events*** • ***Other Adverse Events*** ***Sorafenib***
Month 1 Visit-Arm 2	• ***Protocol Specific Adverse Events*** • ***Other Adverse Events*** • ***Lab Results*** • ***RT Administration Form*** • ***RT Treatment if was RT administered="yes"*** • ***Protocol Specific RT if was RT administered="yes"***
Month 2 Visit	• ***Lab Results*** • ***Protocol Specific Adverse Events*** • ***Other Adverse Events*** ***Sorafenib***
Month 3 and 6 month visit	• ***Lab Results*** ***Sorafenib*** • ***Patient Contact***

	• ***Followup*-if Patient able to be Contacted =“yes”** • ***Primary Cause of Death Form* – if Patient’s Vital Status = “dead”** • ***Disease Assessment Form* – if Documented clinical assessment = “yes”** • ***New Primary Cancer Form* – if New Primary Cancer =“yes”** • ***Non-protocol Treatment* Form – if patient started on non-protocol cancer therapy =”yes”** • ***Adverse Event Form/ Protocol Specific Adverse Events/Other Adverse Events* - if new or continuing adverse events=“yes”** • **Salvage RT-if salvage RT=“yes”** • ***EQ-5D/FACT-HEP*- if consented to QOL**
Month 4 visit and monthly as long as Sorafenib is being administered	• ***Lab Results*** • ***Other Labs*** • ***Protocol Specific Adverse Events*** • ***Other Adverse Events*** ***Sorafenib***
Month 9 visit	• ***Lab Results*** • ***Protocol Specific Adverse Events*** • ***Other Adverse Events*** • ***Followup Form*-if Patient able to be Contacted =“yes”** • ***Primary Cause of Death Form* – if Patient’s Vital Status = “dead”** • ***Disease Assessment Form* – if Documented clinical assessment = “yes”** • ***New Primary Cancer Form* – if New Primary Cancer =“yes”** • ***Non-protocol Treatment* Form – if patient started on non-protocol cancer therapy =“yes”** • **Protocol Specific Adverse Events** • **Other Adverse Event- if new or continuing adverse events=“yes”** • **Salvage RT-if salvage RT=“yes”**
Month 12 visit	• ***Lab Results*** • ***Protocol Specific Adverse Events*** • ***Other Adverse Events*** • ***Followup Form*-if Patient able to be Contacted =“yes”** • ***Primary Cause of Death Form* – if Patient’s Vital Status = “dead”** • ***Disease Assessment Form* – if Documented clinical assessment = “yes”** • ***New Primary Cancer Form* – if New Primary Cancer =“yes”** • ***Non-protocol Treatment* Form – if patient started on non-protocol cancer therapy =“yes”** • ***Adverse Event Form*- if new or continuing adverse events=“yes”** • **Salvage RT-if salvage RT=yes** • ***EQ-5D/FACT-HEP*- if consented to QOL**
Month 15 and q 3 months	• ***Lab Results***

	• ***Protocol Specific Adverse Events*** • ***Other Adverse Events*** • ***Followup Form*-if Patient able to be Contacted =“yes”** • ***Primary Cause of Death Form* – if Patient’s Vital Status = “dead”** • ***Disease Assessment Form* – if Documented clinical assessment = “yes”** • ***New Primary Cancer Form* – if New Primary Cancer =“yes”** • ***Non-protocol Treatment* Form – if patient started on non-protocol cancer therapy =“yes”** • ***Adverse Event Form*- if new or continuing adverse events=“yes”** • **Salvage RT-if salvage RT=“yes”**

12.3 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.5 for account access and installation instructions) (13-MAY-2019)

Pre Randomization Scan (All Patients)

Item	**Due**
Preliminary Dosimetry Information (DD)	
Digital Data Submission – Diagnostic or planning CT or MRI obtained within 28 days prior to registration, include the following	Within 1 week of randomization for Arm 1 patients only and arm 2 patients who do not end up having radiation therapy
• Contours of liver and GTV	
• Volume (cc) of liver minus GTV (>700 cc non-tumor liver recommended)	
• Calculation of GTV/(liver including GTV) (80% recommended)	

ARM 2 ONLY

Item	**Due**
Preliminary Dosimetry Information	
Digital Data Submission –Treatment Plan, including multiphasic CT and /or MRI submitted to TRIAD exported from treatment planning machine by Physicist	Within 1 week of start of RT
Digital data submission includes the following:	
• CT data, critical normal structures, all GTV, CTV, and PTV contours	
• Digital beam geometry for initial and boost beam sets	
• Doses for initial sets of concurrently treated beams	
• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the table in Section 6.5. • *The “RTOG 1112 Datasheet” is available in the Forms section of the RTOG1112 page of the CTSU website.* Submit via TRIAD with the digital data listed above.	
Upon submission of the digital data via TRIAD, complete an online digital data transmission form located in the Forms section on the web site at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1112	
Final Dosimetry Information	Within 1 week of
Radiotherapy Form	

Daily Treatment Record	RT end
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES AND IGRT DATA WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	

NOTE: Copies of simulation and IGRT imaging and the complete RT daily treatment record for the previous original EBRT will be kept by the institution and only submitted if specifically requested.

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

13.1.1 Primary Endpoint

Overall survival *(failure is death due to any cause)*

13.1.2 Secondary Endpoints

- Time to progression (failure is defined per Section 11.3)
- Progression free survival (failure is progression or death due to any cause)
- Toxicity: using Common Toxicity Criteria (CTCAE) version 4.0.
- Vascular thrombosis response
- Health Related Quality of Life [measured by the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep)]
- Quality adjusted survival

13.2 Stratification (8/26/14)

Patients will be stratified before randomization with respect to Vascular involvement (IVC/main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none), Hepatitis (B or B and C vs. C vs. other), Site (North American vs. non-North American), and HCC volume/liver volume (<10% vs. 10-40 vs. >40%). The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

13.3 Sample Size and Power Justification (25-MAR-2020)

13.3.1 The sample size calculations are based on the primary hypothesis that SBRT followed by sorafenib will increase overall survival as compared to sorafenib alone for patients with hepatocellular carcinoma. It is projected that 75% of the accrual will come from North American sites and 25% of the accrual will come from non-North American sites. It is expected that approximately two-thirds of accrual will be patients with vascular thrombosis while one-third will be patients without vascular thrombosis.

The sorafenib alone control arm median overall survival time (MST) is estimated to be 10.5 months, based on the SHARP sorafenib arm MST of 10.7 months (Llovet 2008) and a recent study of 1073 HCC patients randomized to sorafenib versus sunitinib; the median overall survival time (MST) of the patients in the sorafenib arm was 10.0 months (versus 8.1 in the sunitinib arm) [Cheng 2011]. Approximately 75% of these patients were Asian-Pacific, demonstrating that outcomes in Asia have improved since the original Asian-Pacific sorafenib randomized trial (where MST was 6.5 months for sorafenib alone [Cheng 2009]).

The RT sorafenib combination arm MST is hypothesized to be 14.5 months, based on the Toronto RT alone MST of 17.0 months (Bujold 2012) in 102 patients with advanced HCC treated with RT alone on study, as well as a retrospective study of RT and sunitinib from Taiwan with a MST of 16 months (Chi 2010). Other reports of RT alone for HCC patients with portal vein thrombosis demonstrate a range of MSTs from 10 to 15 months, in the absence of sorafenib.

The required sample size for the primary endpoint of OS is based on the following conditions:

- OS times are exponentially distributed with (at least approximately) constant hazards in both treatment arms

- The control arm will have a median OS of 10.5 months (monthly hazard of 0.066)
- The experimental arm will have a median OS of 14.5 months (monthly hazard of 0.0478)
- Hazard ratio (experimental/control) = 0.72
- One-sided test at $\alpha = 0.05$
- Statistical power of 80%
- 7 years of accrual (post ramp-up) with 1 year of follow-up
- Three interim significance tests and a final test are planned using the Haybittle-Peto (Lan 1983; O'Brien 1979) rule for efficacy and a more aggressive futility rule suggested by Weiand et al (1994).

A total of 264 evaluable patients, using the group sequential design method (Pocock 1977) with 3 interim analyses, will provide the 238 OS events required to determine if the addition of SBRT to sorafenib alone improves overall survival from 10.5 to 14.5 months (HR=0.72). Given the conditions above, and adjusting for ineligible/lost patients or patients that cannot meet the RT planning requirements, **a total sample size of 292 patients** will be required to be accrued uniformly over 7 years, post ramp-up period, with an additional 1 year of follow-up.

13.3.2 Patient Accrual

Patient accrual is projected to be 3 cases per month, with a ramp-up period in the first 6 months with no projected accrual. Following this ramp-up period, accrual will be completed in 7 years.

Projected accrual was based on a survey submitted in June 2011 by the RTOG to all full RTOG members, the members of the RTOG GI Steering Committee and interested Asian centers. In brief, there were 43 respondents, including the 2 Asian centers. Twenty-eight centers planned to definitely open the study; 22 of these centers are already credentialed for RTOG lung or liver SBRT studies (excluding the 2 Asian centers). An additional 13 centers were considering opening the study (all of these centers were credentialed for RTOG lung or liver SBRT studies). Based on the 22 credentialed RTOG non-Asian centers, 12 patients per month were estimated to be accrued to this study. Including the Asian centers, 17 patients per month were estimated to participate. Accounting for some overestimation and lower than expected accrual in prior HCC studies, the actual expected accrual is 3 patients per month.

If the total accrual during months 13 through 18 of the study is ≥ 50% of the targeted accrual (18 or more cases), then the accrual will have met the NCI-CTEP Ph III accrual guidelines and will continue. If the total accrual during months 13 through 18 of the study is ≤ 20% of the targeted accrual (≤ 7 cases in total), then the protocol will be discontinued per NCI-CTEP accrual guidelines for phase III studies. If the total accrual during months 13 through 18 is between 21% and 49% (8 to 17 cases), then the protocol will continue to accrue subjects and will be evaluated again at the end of month 24. If the accrual during months 22 through 24 is at least 50% of the targeted accrual (≥ 9 cases in total), the NCI-CTEP accrual guidelines for phase III studies will have been met and the study will continue accrual; otherwise, the study will be discontinued.

13.4 Power Information for Health Reported Quality of Life – FACT-Hepatobiliary Module (FACT-Hep) (25-MAR-2020**)**

The Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep) will be used to measure HRQOL. Protocol-eligible patients will be included in the QOL analysis only if they have provided baseline and at least one subsequent measurement. The FACT-Hep will be collected on all cases participating in this portion of the trial and will be collected at 4 time points: baseline, 3 months, 6 months, and 12 months post initiation of protocol therapy.

13.4.1 The primary HRQOL endpoint will be to determine whether patients treated with SBRT and sorafenib have an improved FACT-Hep score from baseline to 6 months, as measured by the proportion of patients on each treatment arm with improvement, defined as an increase in the FACT-Hep score of at least 5 points (minimally important difference), as compared to patients receiving sorafenib alone. The power calculations shown below cover a number of possible

proportions for improvement over the control arm. The power calculations are all based on a 1-sided, α=0.05, chi-squared test and the listed patient participation rate (PPR) of the 320 evaluable patients required for the overall study.

Power Calculations for FACT-Hep Score

p_0	p_a	Power (84% PPR n/arm=111)	Power (74% PPR n/arm=98)	Power (64% PPR n/arm=85)
0.10	0.25	91	87	83
0.10	0.30	98	97	95
0.20	0.35	81	76	71
0.20	0.40	95	93	89
0.30	0.45	75	70	65
0.30	0.50	92	89	85
0.40	0.55	73	68	62
0.40	0.60	91	88	84
0.50	0.65	73	67	63
0.50	0.70	92	89	85

*If the participation rate is higher, there will be more power to detect the hypothesized differences; if the participation rate is lower, there will be less power.

13.4.2 A secondary HRQOL endpoint will be to determine whether patients treated with SBRT and sorafenib have an improved FACT-Hep score, as measured by the proportion of patients on each treatment arm with improvement, defined as an increase in the Trial Outcome Index (TOI) score of at least 7 points (minimally important difference), as compared to patients receiving sorafenib alone. The TOI scale consists of the physical well-being and functional well-being subscales from the FACT-G with hepatobiliary module. The power calculations, with the same assumptions, are the same as shown in Section 13.4.1.

13.4.3 Another secondary HRQOL endpoint will be to determine whether patients treated with SBRT and sorafenib have an improved NCCN/FACT-Hep Symptom Index (FHSI-18) score, as measured by the proportion of patients on each treatment arm with improvement, defined as an increase of at least 2 points (minimally important difference), as compared to patients receiving sorafenib alone. The FHSI-18 has a total of 18 items assessing common symptoms when treating advanced hepatobiliary disease. The power calculations, with the same assumptions, are the same as shown in Section 13.4.1.

13.5 **Analysis Plan** (26-MAY-2022)

All analyses will be done based on the assigned treatment arm for all eligible patients entered.

13.5.1 Statistical Methods

Overall Survival

Overall survival (OS) will be estimated by the Kaplan-Meier method (Kaplan 1958). The distribution of OS estimates between the 2 arms will be compared using the log rank test (Mantel 1966). OS time will be measured from the date of randomization to the date of death or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS.

Progression-Free Survival

Progression-free survival (PFS) will be estimated by the Kaplan-Meier method (Kaplan 1958). The distribution of PFS estimates between the 2 arms will be compared using the log rank test (Mantel 1966). PFS time will be measured from the date of randomization to the date of first failure or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with PFS.

Time-to-Progression (TTP)

Time-to-progression (TTP) will be estimated by the cumulative incidence method (Mantel 1966). The distribution of TTP estimates between the 2 arms will be compared using Gray's test (Gray 1988). TTP time will be measured from the date of randomization to the date of first failure or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with TTP.

13.5.2 Interim Analysis to Monitor the Study Progress

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

- Patient accrual rate with a projected completion date (while the study is still accruing)
- Total patients accrued
- Distributions of important pretreatment and prognostic baseline variables
- The frequencies and severity of adverse events by treatment arm
- Compliance rates of treatment delivery

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

13.5.3 CDUS Reports

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

13.5.4 Significance Testing for Early Termination and/or Reporting

Unacceptable Toxicity

To address the safety of SBRT followed by sorafenib, the rate of unacceptable adverse events will be evaluated on both treatment arms. This analysis will focus on the following AEs occurring within 90 days from the start of protocol treatment definitely or probably related to protocol treatment:

a) grade 4 or 5 hepatic
b) grade 4 or 5 gastrointestinal
c) grade 4 thrombocytopenia associated with any bleeding or grade 5 thrombocytopenia
d) Any grade 5 treatment-related adverse event

Assuming no more than a 10% rate of the above AEs on the sorafenib alone arm, the study chairs have determined that an increase to a rate of 30% or greater on the SBRT followed by sorafenib arm will be considered to be unacceptable. One-hundred and fifty-four patients provide 90% power to detect an increase in the rate of specified AEs from 10% to at least 30% with a 1-sided alpha of 0.05, using a Chi-squared test for difference in proportions. If the p-value from the test described above is ≤ 0.05, the conclusion will be that the treatment-related unacceptable AE rate for the SBRT followed by sorafenib arm is at least 30% and accrual to the study will be stopped.

Primary Endpoint: Overall survival (OS)

Three interim significance tests of treatment difference are planned. The timing of the interim analyses will be based on OS failure events, as described in Section 13.1.1. The maximum number of events required for the study is 238. Under the alternative hypothesis that the addition of SBRT will increase median OS from 10.5 months to 14.5 months, the projected numbers of events and the nominal significance levels for rejecting the H_0 or the H_1 for each of these two interim analyses are shown in the table below:

Nominal Significance Levels for Interim Analyses

Interim Analysis	Efficacy: Reject H_0 if $p(H_0) \leq$	Futility: Reject H_1 if $Z(H_0) \leq$	# Events (%)
#1	0.001	0	98 (41%)
#2	0.001	0	143 (60%)
#3	0.001	0.385	190 (80%)

At each planned interim analysis, the p-value from the log-rank test assessing treatment efficacy and the Z-score assessing treatment futility with respect to OS will be compared to the nominal significance/critical levels in the table above. If the computed p-value is less than or equal to the nominal significance level boundary for rejecting the H_0 (efficacy), then accrual to the trial will be stopped (if applicable), it will be concluded that the OS with SBRT and sorafenib (Arm 2) is significantly higher than sorafenib alone (Arm 1) and the results will be reported. If the Z-score is less than or equal to the nominal critical level boundary for rejecting the H_1 (futility), then accrual to the trial will be stopped (if applicable) and it will be reported that it cannot be concluded that the OS with SBRT and sorafenib (Arm 2) is significantly higher than sorafenib alone (Arm 1). Otherwise, accrual to the trial or follow-up (as applicable) will continue until the next interim or final analysis.

In addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events, and compliance with protocol treatment, blinded efficacy results will be reported to the NRG Oncology data monitoring committee (DMC), following the required number of events for each planned interim analysis.

13.5.5 Analysis for Endpoints Related to HRQOL

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

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

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

FACT-Hep Scoring and Analysis

The FACT-Hep will be scored per the FACT-Hep Scoring Guidelines (Version 4 **www.facit.org**), with higher scores indicating better QOL.

The primary objective in the HRQOL analysis is improvement in the FACT-Hep score, defined as an increase of 5 points or more from baseline to the assessment at 6 months from the start of protocol therapy. Chi-squared tests will be used to test the null hypothesis that the proportion of patients categorized as “improved” will be the same for the 2 treatment arms, versus the alternative hypothesis that the proportion of patients categorized as “improved” is higher for the SBRT+sorafenib arm.

Improvement in the FACT-Hep score, as defined above, will also be compared between the treatment arms for changes from baseline to both 3 and 12 months with the same methodology as listed above.

Correlation of baseline FACT-Hep and survival will be evaluated.

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

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

To examine trade-offs between the survival time and QOL, they will be combined for each patient into a single measurement: quality-adjusted life years (QALY). If (and only if) the primary endpoint hypothesis is substantiated, a quality-adjusted survival analysis will be conducted. The quality-adjusted survival analysis will not be done until after the primary endpoint results are published. QALY is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. QALY will be analyzed at 2 time points: at 6 and 12 months from start of treatment, using the EQ-5D.

13.5.6 Analysis for Reporting the Initial Treatment Results
The primary hypothesis of this study is SBRT and sorafenib will increase the median OS from 10.5 months to 14.5 months as compared to sorafenib alone for patients with hepatobiliary carcinoma. The timing of initial treatment results analysis will be as described in Section 13.5.7 and will include:

- Tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- Distributions of important prognostic baseline variables
- The frequencies and severity of adverse events by treatment arm.
- Compliance rate of treatment delivery
- Observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a significance level of 0.05, given that the 3 interim analyses were carried out per Section 13.5.4. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factor included as a fixed covariate, as well as any factors that show an imbalance between the arms (eg, age, gender, race, Zubrod status, etc.).

13.5.7 Time-Driven Definitive Analysis
The statistical analysis plan changes were done in accordance with the NCI Policy for Major Design Amendments for Ongoing Randomized Clinical Trials. The specifics for the changes were performed by a statistician independent from the trial.

External circumstances have resulted in accrual closure with 177 eligible patients currently enrolled. Due to the limited sample size and observed event rate, coupled with concerns regarding adoption of new therapy among participants, the trial primary endpoint will be reported

at a fixed calendar date (July 1, 2022, or completion of this amendment, whichever is later). The targeted treatment effect (experimental/control HR = 0.72) and alpha level (one-sided 0.05) will remain unchanged from the original design.

The primary endpoint analysis will thus be performed with the number of OS events reported through July 1, 2022 (or completion of this amendment, whichever is later). It is anticipated that at that time, at least 155 OS event will have been observed. The log-rank test with 155 OS events will have 65% power at one-sided alpha 0.05 to detect the targeted treatment effect (experimental/control HR of 0.72).

13.6 Gender and Minorities (23-SEP-2022)

Both men and women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interaction between race/ethnicity and treatment has been considered. It is projected that 80% of the patients will be men and 20% women; 2% will be of Hispanic or Latino ethnicity and 98% will not; racial distribution will be 73% white, 2% black or African American, and 25% Asian. Assuming no differences between the ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference is 64% for males and 21% for females. Assuming no differences between genders or the ethnicities, the statistical power is 60% for whites and 25% for Asians. The projected non-White/Asian accrual rate is too low for any meaningful treatment comparisons. Assuming no differences between the genders, or among the races, the statistical power for detecting the hypothesized treatment difference in non-Hispanic/Latino ethnicity will be 73%. The projected Hispanic/Latino accrual rate is too low for any meaningful treatment comparisons.

The following table lists the projected accrual by gender, ethnic, and racial categories.

Projected Distribution of Gender and Minorities

DOMESTIC

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	0	1	0	1	**2**
Asian	1	4	0	3	**8**
Native Hawaiian or other Pacific Islander	1	0	0	0	**1**
Black or African American	3	8	1	2	**14**
White	10	52	3	9	**74**
More than one race	0	1	0	2	**3**
TOTAL	**15**	**66**	**4**	**17**	**102**

FOREIGN

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian or Alaska Native	0	0	0	0	**0**
Asian	9	41	0	0	**50**
Native Hawaiian or other Pacific Islander	0	0	0	0	**0**
Black or African American	1	5	0	0	**6**
White	24	110	0	0	**134**
More than one race	0	0	0	0	**0**
TOTAL	**34**	**156**	**0**	**0**	**190**

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APPENDIX I
STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (13-MAY-2019)

Pre-Treatment Assessments (may be required for eligibility)	≤360 days prior to study entry	28 days prior to study entry	14 days prior to study entry
Biopsy, cytology ,radiographically confirmed HCC	X		
History/physical*			X
Performance status		X	
TNM stage, BCLC stage			X
Child Pugh score, MELD score			X^
Assessment by radiation oncologist, medical oncologist or hepatologist		X	
CBC w/diff, ANC, platelets			X
Serum creatinine or creatinine clearance, ALT, AST			X
Alpha-fetoprotein		X	
Bilirubin, albumin, INR, ALP, phosphate, sodium, potassium, chloride, magnesium		X	
Calcium		X	
bHCG test (if applicable)			X
Multi-phasic liver CT or multi-phasic liver MRI		X	
CT chest and CT or MR abdomen and CT or MR pelvis, or PET CT chest/abdomen/pelvis		X	
Quality of Life (for consenting patients)	Pre-Treatment		
Tissue banking (for consenting patients)	Pre-Treatment		
Plasma banking (for consenting patients)	Pre-Treatment		
Whole blood banking (for consenting patients)	Pre-Treatment		
Informed consent		X	

*Including ascites, encephalopathy, weight, height, and blood pressure.
^ INR < 28 days can be used for scoring < 14 days
-Continued on next page-

APPENDIX I

STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT AND FOLLOW-UP (25-MAR-2020**)**

Assessments	**SBRT**			**During Sorafenib (Arm 1 and 2)**	**Follow up for ALL Patients** (Arm 1 and 2)**	
	Arm 2 - Weekly (following at least one fraction)	**Arm 2 -** Prior to starting sorafenib, post last SBRT fraction		Monthly (or per local standard of care)	Every 3 months from study entry for 2 years from study entry	Then, every 6 months
History/physical*	X	X		X	X	X
Performance status	X	X		X	X	X
Child Pugh score, MELD score					X	X
Assessment by radiation oncologist, medical oncologist or hepatologist	X	X		X	X	X
Assessment by medical oncologist and/or hepatologist		X		X		
CBC w/diff, ANC, platelets	X			X	X	X
Serum creatinine or creatinine clearance, ALT, AST	X			X	X	X
Bilirubin, albumin, INR, ALP, phosphate, sodium, potassium, chloride, magnesium				X	X	
Calcium					X	
Alpha-fetoprotein					X	X
Multi-phasic liver CT or multi-phasic liver MRI					X (for 2 years then every 6 months)	X
CT chest					X (annually only)	X (annually only)

Adverse event eval (and as needed based on reporting requirements)†	X	X		X	X	X
Quality of Life (for consenting patients)					3, 6, 12 months only	
Plasma and whole blood banking (for consenting patients)					1 and 3 months only (see section 10.2.6)	
Pill diary (do not send to NRG HQ)				Daily during sorafenib		
*Including ascites, encephalopathy, weight, and blood pressure. ** Including patients receiving sorafenib or patients who have discontinued sorafenib. † Including skin toxicity (in and out of RT volumes for SBRT arm). Note: For q monthly tests, +/- 2 week is permitted, and for q 3, 6 and 12 monthly tests, +/- 3 weeks is permitted. Pill diary: *http://www.rtog.org/ClinicalTrials/NonStudySpecificForms.aspx* After patients have been documented to have radiologic PD, the above follow-up is recommended, but not mandatory.						

APPENDIX II

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX III

AJCC Staging System

Edge SB, ed. AJCC Cancer Staging Manual 7th ed. New York, NY, 2010

HEPATOCELLULAR CARCINOMA

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or Multiple tumors no more than 5 cm
T3a	Multiple tumors more than 5cm
T3b	Tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases

Distant Metastases (M)

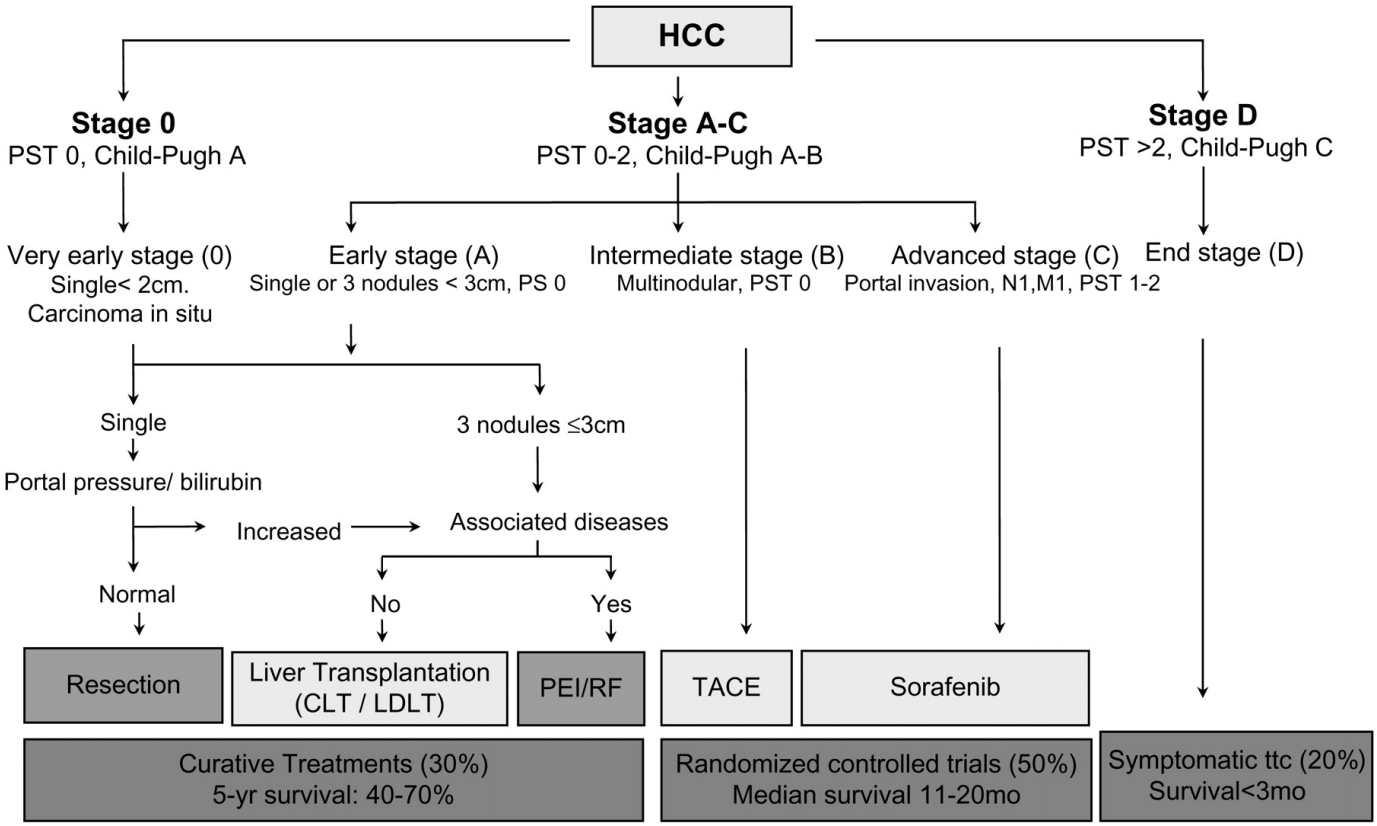
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Stage Grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

APPENDIX IV

BCLC Staging System



APPENDIX V (27OCT2017)

Multi-Phase Hepatocellular Carcinoma Imaging Protocol

Recommended imaging for hepatic CT simulation and follow-up

Multi-phase liver CT protocol using iodinated intravenous (IV) contrast will be obtained at 2.5 or 3 mm slice thickness. The four phase HCC protocol includes a non-contrast CT, arterial (A) phase imaging, portal venous (V) phase imaging and delayed (D) phase imaging. The A phase of imaging demonstrates hypervascularity of HCC. The V phase is often best for visualization of vascular thrombi. The D phase imaging demonstrates washout of HCC. All four phases are recommended for use at baseline diagnosis for HCC; A/V/D phase imaging is recommended for follow-up of HCC patients, with all phases including the whole liver and V or D phase including the entire abdomen. For CT simulation, at least 2 phases of imaging are recommended (A/V or A/D), with all phases including the whole liver and one phase including enough of the abdomen to develop a patient model for radiation planning.

All multi-phase imaging is recommended to be obtained in breath hold, with the arms up when possible.

The timing of imaging after IV contrast administration: Bolus Tracking technique

The timing varies between 16 and 64 detector scanners (with image acquisition occurring faster on a 64 detector CT scanner). It is recommended that IV contrast (e,g. Visipaque) 2cc/kg to a max of 180cc be injected @ 5cc/second using a minimum of 20G antecubital. IV bolus tracking, a commercially available technique, is recommended for use to control for variations in cardiac circulation time, to ensure the images are obtained during the correct phases of contrast enhancement. As is standard practice, a cursor is placed in the aorta at the level of the origin of the celiac axis and is used to detect when contrast arrives in the abdominal aorta and raises the attenuation value to 100 Hounsfield Units. For a 64 detector scanner, A, V and D phase scanning occurs 20, 60 and 180 seconds, respectively, after the 100HU threshold is reached.

MR imaging

Gadolinium or Primovist/Eovist (Gd-EOB-DTPA) enhanced liver MRI may be utilized to facilitate target delineation and should be used if there is a contraindication to IV CT contrast. It is recommended that non-contrast-enhanced and dynamically obtained T1 weighted sequences at a slice thickness of 7mm at maximum be used. Details of the imaging protocol should be developed in collaboration with the diagnostic radiology department.

If a patient has contraindications to CT and MR IV contrast, then non-contrast T1 weighted MR images may be used for target delineation, only if T1 weighted images demonstrate the HCC with clearly defined edges.

APPENDIX VI (27OCT2017)

Child Pugh Classification of Liver Function

Clinical and Biochemical Parameters	Score (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy	None	1 - 2	3 - 4
Ascites	None	Slight	Moderate
Non clinical trace ascites on imaging only is not mandated to be included as "mild ascites" (2 points). Instead it may receive 1 point on this study.			
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
INR*	< 1.7	1.7 - 2.3	> 2.3
Bilirubin (mg/dL)	1 - 2	2 - 3	> 3

* INR = International Normalized Ratio for Prothrombin Time

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

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

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

Reference: Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma exchange blood transfusion. N Engl J Med 1966; 274 (9): 473-481

APPENDIX VII

Model for End-Stage Liver Disease (MELD) Score

The MELD score is based on the patient's bilirubin, creatinine and the INR to predict survival. It is calculated according to the following formula:

MELD = 9.57 * ln(serum creatinine in mg/dl) + 3.78 * ln(total serum bilirubin in mg/dl) + 11.2 * ln(INR) + 6.43

If any value is less than one, it should be given a value of 1.

Reference; Kamath PS, Kim WR (March 2007). "The model for end-stage liver disease (MELD)". Hepatology 45 (3): 797–805.

APPENDIX VIII (8/26/14)

Veff CALCULATION

Use of effective liver volume (Veff) to aid in dose prescription is permitted if available, but it is not to be the primary tool used for dose allocation. The following table is used as a guide. If there are discrepancies in the Veff and mean liver dose (MLD) for the prescription dose allocation, MLD will be used for dose allocation. A call to the clinical PI or physics PI is recommended if this occurs.

Liver Veff	Planned Prescription Dose (Gy)	If the allowed Veff is exceeded at this planned dose
< 25%	50	Reduce to 45 Gy and re-evaluate
25 - 29%	45	Reduce to 40 Gy and re-evaluate
30 - 34%	40	Reduce to 35 Gy and re-evaluate
35 - 44%	35	Reduce to 30 Gy and re-evaluate
45 - 54%	30	Reduce to 27.5 Gy and re-evaluate
55 - 64%	27.5	Ineligible

Veff must be calculated using the methods described in the references below. The equation below may be used.

$$Veff = \sum_i \Delta v_i \left(\frac{d_i}{d_{ref}} \right)^{\frac{1}{n}}$$

where Δv_i is a volume bin of a differential DVH, d_i is the dose to that volume, and d_{ref} is the reference dose and n is the volume effect parameter (equal to 0.97 in this application).. **The prescription dose is used as the reference dose in this study.**

1. Kutcher GJ BC, Brewster L et al. Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. Int J Radiat Oncol, Biol, Phys 1991;21:137-146.
2. Dawson LA, Eccles C, Craig T. Individualized Image Guided Iso-NTCP based Liver Cancer SBRT. Acta Oncol. 45: 856 – 864, 2006.

APPENDIX IX (27Oct2017)
APPENDICES FOR NRG Oncology BIOSPECIMEN COLLECTION

NRG Oncology
Blood Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For non-urgent FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco – Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (ST) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or phone: 415-476- 7864 or Fax: 415-476-5271.**

APPENDIX IX (27OCT2017)

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma or whole blood *(as specified by the protocol)*:

- **Kit contents (Note: Sites are responsible for providing blood draw tubes):**
- Thirty (30) 1 ml cryovials for plasma and serum – all time points
- Three (3) 2 ml cryovials for whole blood
- Biohazard bags (7) and Absorbent shipping material (7)
- One Styrofoam container (inner) and Cardboard shipping (outer) box per case
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube (one 10 ml or two 5ml)

- ❑ Label five 1ml cryovials for the serum collected. Label them with the study and case number, collection date, time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. Aliquot a minimum of 0.5 ml serum into each of the five cryovials as necessary for the serum collected, labeled with study and case numbers, collection date, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

(B) Plasma (if requested): Purple Top EDTA tube #1 (one 10 ml or two 5ml)

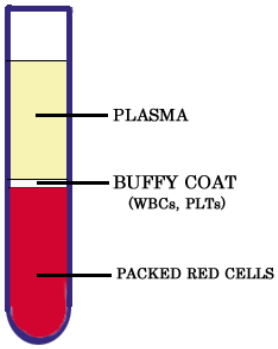
- ❑ Label five 1ml cryovials for the plasma collected. Label them with the study and case number, collection date, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma into each of the five cryovials as necessary for the plasma collected, labeled with study and case numbers, collection date, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS (continued)



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2 (one 5 ml or 10ml tube)

- ❑ Label three 1ml cryovials as necessary for the whole blood collected. Label them with the study and case number, collection date, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0-2.0 ml blood into three 2ml cryovials as necessary for the blood collected, labeled with study and case numbers, collection date, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze tubes upright immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to batch ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

(continued on next page)

BLOOD COLLECTION KIT INSTRUCTIONS (continued)

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

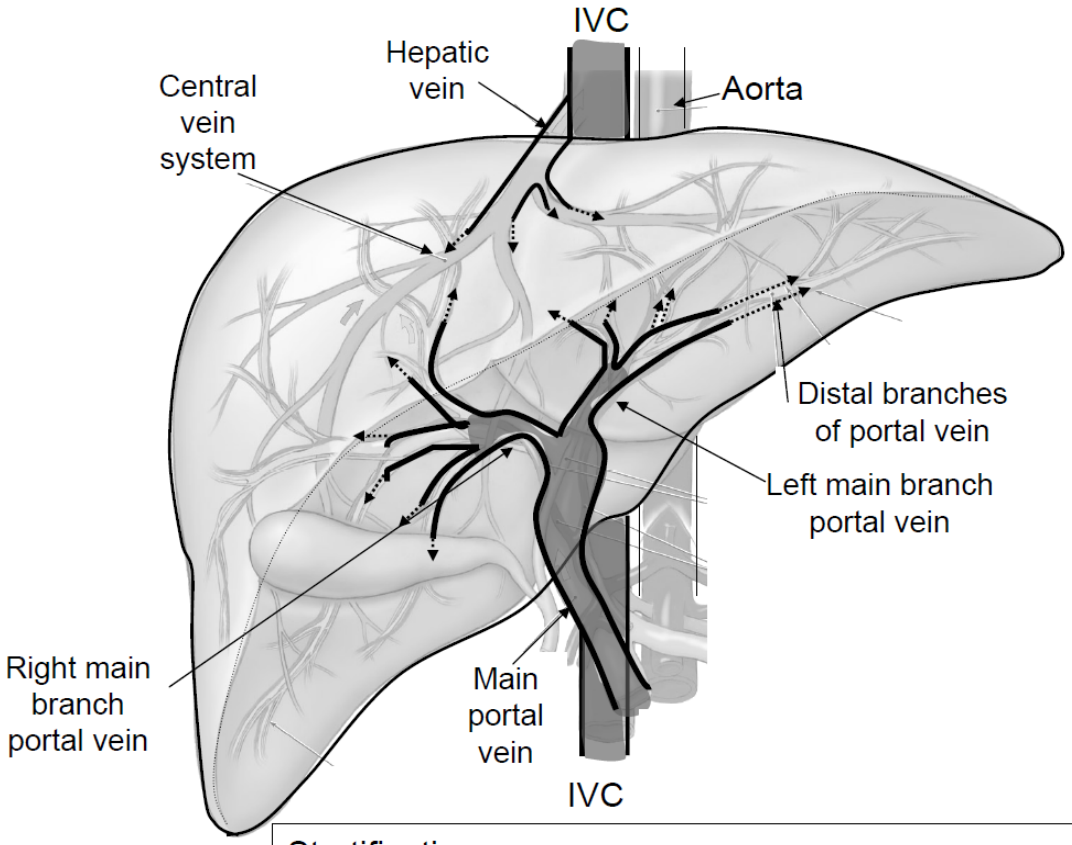
Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank – San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476- 7864 or e-mail: NRGBB@ucsf.edu

APPENDIX X

VASCULAR THROMBOSIS STRATIFICATION DIAGRAM

One stratification factor is degree of vascular thrombosis. The three strata are:
1) Tumor thrombosis involving the IVC, the main portal vein or the right or left main branch portal vein. This includes any thrombi involving these vascular structures at least partially, defined as involving any of the IVC, main portal vein or the right or left main branches of the portal vein. The right and left main branches of the portal vein are the first branches off the main portal vein, up to the first bifurcation of the right and left portal veins, as shown in the diagram below.
2) Any other thrombosis (e.g. involving the more distal portal veins or hepatic veins)
3) No vascular thrombosis.



Stratification:
1. IVC, main portal, right or left main branch portal thrombosis
2. Any other vascular thrombosis (e.g. distal portal, hepatic)
3. No vascular thrombosis