Sequential TransArterial chemoembolization and stereotactic RadioTherapy Followed by ImmunoTherapy for downstaging hepatocellular carcinoma for hepatectomy (START-FIT)

Sponsor: The University of Hong Kong

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Protocol-specific Sponsor contact information can be found in the Investigator(s) Study File.

Laboratory-related information can be found in the Investigator(s) Study File, Section named 'Laboratory Documents

Investigator(s) Signatory

I agree to conduct this Clinical Study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

_____ _____

Typed Name: Dr. CHIANG Chi Leung Date

Title: Clinical Assistant Professor

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1. BACKGROUND

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide and ranks the third on the incidence of cancer-related death. There are more than 500,000 new cases diagnosed annually worldwide. The incidence and prevalence of HCC are on rising trend with the majority of the disease burden is in Asia where viral hepatitis B is endemic. (1)

Surgical resection, radiofrequency ablation (RFA) and liver transplantation (LT) represent the only chance of cure for HCC patients. Despite more aggressive surgical approach has been adopted in most Asian countries, yet curative interventions remain only amendable in 30% of patients. (2) Most patients are diagnosed with intermediate or advanced stage diseases; the long-term cure rate is only 0-10%. For those with inoperable disease, trans-arterial chemoembolization (TACE) is the most widely used local therapy and is the standard of care for intermediate stage HCC. (3-4) Our previous randomized trial is one of the landmark studies to demonstrate the survival benefit in these patients. (3) However, its efficacy is limited in those with large tumor burden and vascular involvement. Shim et al. reported the 2-year survival of HCC patients receiving TACE is 42% versus 0% for tumor sizes of 5-7cm and ≥ 8cm, respectively. (5) Tumor response is even more rarely seen in patients receiving oral multi-kinase inhibitors. (6-7) To date, there is no effective down-staging strategy in unresectable HCC due to limited response of various therapeutic approaches. There is a huge unmet need for more effective therapy for locally advanced HCC.

1.1 SBRT

Until recently, external radiotherapy has a limited role in the management of HCC. Stereotactic body radiotherapy (SBRT) has been introduced to treat liver malignancy since l990s. (8) SBRT refers to the utilization of a few fractions of a potent dose of highly conformal radiation with excellent geometric precision, therefore able to deliver tumoricidal dose to the tumor while sparing the adjacent normal structures. Several prospective series have demonstrated that a local control rate of 87-100% at 1-year, overall survival of 60-69% at 2-year and limited toxicity. (9-12) Data from literature and our group suggested that SBRT might offer a better response rate and more durable control than TACE in locally advanced HCC patients. Large-scale randomized phase III trial is ongoing in evaluating the combining SBRT and systemic therapy Sorafenib versus Sorafenib alone. (13)

1.2 TACE Plus SBRT

Further, meta-analysis has demonstrated TACE plus radiotherapy (RT) are more therapeutically beneficial than TACE alone. (14) There are several reasons for the potential synergism between the two treatment modalities: RT can kill the residual cancer cells after TACE, especially those at the tumor periphery that remain viable through the blood supply from the collateral circulation (15); secondly, TACE damages large numbers of cancer cells, which promotes the residual cells from a non-proliferative phase into cell proliferation, and thus become more radiosensitive (16); thirdly, TACE also decreases the tumor volume, which in turn reduces the radiation field and adverse events (17); in addition, the retention of chemotherapeutic agents from embolization in liver tumor cells has a radio-sensitizing effect

and accelerates tumor necrosis (18); finally, our group has reported the lipiodol enabled more accurate localization of HCC during SBRT. (19)

Our team had reviewed 73 intermediate to advanced stage HCC patients who received a single dose of TACE followed by SBRT. The median size of the tumor is 11.2cm, and 25% of them have the vascular invasion. The objective response rate (ORR) was 68%, the 1-year local control (LC) rate was 93.6%, the median progression-free survival (PFS) was 7.2 months, and median overall survival (OS) was 19.8 months. Twelve (16.4%) patients had treatment response were amendable for subsequent surgical resection, median OS was not yet reached for those who have operated. There was no patient developed radiation-induced liver disease (RILD) (20). Further, we also retrospectively compared the outcomes of TACE plus SBRT versus TACE in patients with intermediate HCC using propensity score matching (1:2). There was a significant improvement in median OS after TACE+SBRT when compared to TACE alone (23.9 months vs. 10.4 months, $p<0.001$). Also, there was a significant improvement of 3-year PFS (26.6% vs. 8.3%, $p=0.03$). (Unpublished data)

In a recently published phase II randomized trial, 90 unresectable HCC patients with vascular invasion were randomized to receive TACE+RT versus Sorafenib; the TACE+RT was associated with significantly better 12-week PFS rate (77.8% vs. 26.7%; $p<0.001$), median time to disease progression (30 weeks vs. 8 weeks; $p<0.001$), and median OS (55 weeks vs. 43 weeks; $p=0.04$) than Sorafenib alone. (21)

Taken together, combined TACE and SBRT is a more powerful local treatment than TACE alone, yet distant control remains a key challenge for unresectable HCC patients.

1.3 Immune Checkpoint Inhibitors (ICI)

Immune checkpoint inhibitors (ICI) represent another breakthrough in the management of advanced HCC patients. Preclinical data have shown that HCC's tumor microenvironment is immunosuppressive; (22) the overexpression of inhibitory proteins PD-1 and CTLA-4 on the exhausted T-cells has rendered the checkpoint inhibitors a promising therapeutic option. (23)

The first published report on checkpoint inhibition in HCC is a phase II trial using the CTLA-4 inhibitory antibody tremelimumab. The trial enrolled 21 patients with hepatitis C–related cirrhosis. Among 17 evaluable patients, three (18.0%) had a partial response, and an additional 10 (58.8%) had stable disease, with a median time to progression of 6.5 months. However, nearly half (45%) of all patients experienced grade 3 or higher toxicity, primarily transaminase elevations. Typical immune-related toxicities such as rash (65%) and diarrhea (30%) were common, but no patients required corticosteroid treatment for toxicity. (24) Later, the checkmate-040 phase I/II trial was recently published, among 214 of advanced HCC patients received anti-PD1 Nivolumab 3mg/Kg every 2 weeks, the objective response rate (ORR) was 20%, the median duration of response was 9.9 months, and the toxicity profile was manageable. (25) The favorable ORR and durability of response have lead to FDA accelerated approval of Nivolumab in HCC patients who have previously been treated with Sorafenib.

There is evidence of synergistic effect from the combination of immunotherapy regimes with SBRT. Radiation could induce immunogenic cell death and convert the irradiated tumor into an in-situ vaccine to prime the immune system for the checkpoint inhibition. (26) Pre-clinical data have demonstrated that the combination of SBRT and checkpoint inhibition resulted in

better local tumor regression and abscopal (out-of-field) effect when compared with the use of either single modality treatment. (27-28) Early clinical reports in melanoma and lung cancer patients have provided further support for the efficacy and safety of this novel combination. (29-30). In the randomized phase III PACIFIC trial in stage III non-small cell lung cancer, patients were randomized to receive anti-PD-L1 Durvalumab or placebo after completion of chemo-radiation, the PFS was significantly longer in patients receiving checkpoint inhibitors (16.8 months versus 5.6 months, $p<0.0001$). (31)

Based on our pilot work and the recent evidence, we propose a phase II trial to test the concept of combined TACE and SBRT followed by immune checkpoint inhibitor as a neo-adjuvant treatment in unresectable HCC patients.

2. STUDY OBJECTIVES

2.1 Primary Objective

1. To assess the number of patients amenable to curative surgical interventions in HCC patients treated with combined TACE and SBRT followed by Avelumab

2.2 Secondary Objectives

1. To assess the number of patients amenable to curative surgical interventions and/or achieve radiological complete response in HCC patients treated with combined TACE and SBRT followed by Avelumab
2. To assess the objective response rate in HCC patients per mRECIST treated with combined TACE and SBRT followed by Avelumab
3. To evaluate the time-to-progression (TTP), progression-free survival (PFS) and overall survival (OS) in HCC patients treated with combined TACE and SBRT followed by Avelumab
4. To measure the toxicities in HCC patients treated with combined TACE and SBRT followed by Avelumab
5. To evaluate the patient-reported quality of life (QoL) treated with combined TACE and SBRT followed by Avelumab
6. To describe the pathological response among HCC patients amenable to surgery after receiving combined TACE and SBRT followed by Avelumab
7. To assess the disease control rate (DCR) in HCC patients treated with combined TACE and SBRT followed by Avelumab
8. To assess the local control rate among HCC patients treated with combined TACE and SBRT followed by Avelumab
9. To evaluate the duration of response among HCC patients responded to combined TACE and SBRT followed by Avelumab
10. To describe the pattern of failure at the time of progression

11. To assess the objective response rate in HCC patients per RECIST 1.1 treated with combined TACE and SBRT followed by Avelumab
12. Collection of bio-specimens for future correlative studies in patients treated with TACE and SBRT followed by Avelumab

2.3 Study Design

This study is a prospective phase II, single arm clinical trial assessing the efficacy and safety of the sequential administration of trans-arterial chemo-embolization (TACE) and stereotactic body radiotherapy (SBRT) followed by Avelumab in intermediate to advanced hepatocellular carcinoma (HCC) patients.

2.4 Study Participants

A total of 33 patients will be accrued to assess the potential benefit of combined TACE and SBRT followed by Avelumab.

3. ELIGIBILITY CRITERIA (CHECKLIST FORM A)

3.1 Inclusion Criteria

1. Diagnosis of unresectable HCC confirmed pathologically or made according to American Association for the Study of Liver Diseases (AASLD) practice guideline 2010: patients with cirrhosis of any etiology and patients with chronic hepatitis B (HBV) who may not have fully developed cirrhosis, the presence of liver nodule >1cm and demonstrated in a single contrast-enhanced dynamic imaging [magnetic resonance imaging (MRI)] of intense arterial uptake and “washout” in portal venous and delayed phases.
2. Male or female subjects with age: 18-80 years old
3. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
4. Tumor size 5-25cm and number of lesions ≤3
5. Portal vein involvement (Vp1-3) is allowed: Vp1, presence of a tumor thrombus distal to, but not within, the second-order branches of the portal vein; Vp2, presence of a tumor thrombus in the second-order branches of the portal vein; Vp3, presence of a tumor thrombus in the first-order branches of the portal vein. (32)
6. Child-Pugh liver function class A-B7
7. Liver volume minus intrahepatic GTV >700 cc.
8. Minimal distance from GTV to stomach, duodenum, small or large bowel >1 cm.
9. No prior systemic therapy nor immunotherapy
10. No prior trans-arterial chemo-embolization (TACE)
11. No prior radiotherapy to the liver or selective internal radiation (SIRT)

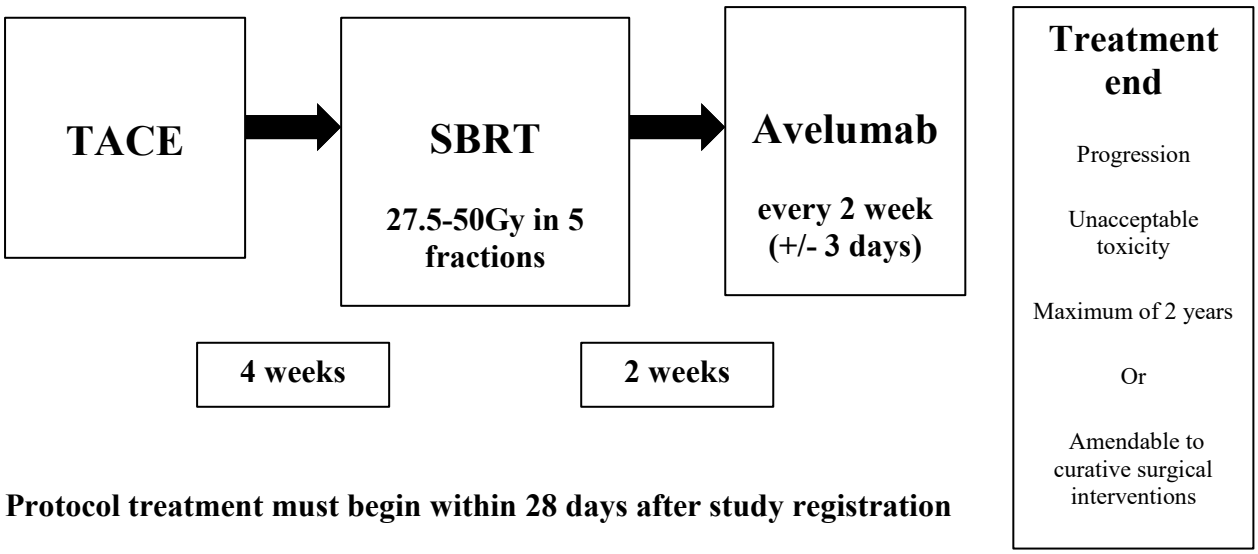
12. Written informed consent obtained for clinical trial participation and providing archival tumor tissue, if available.
13. Subjects with confirmed concomitant HBV infection (defined as HBsAg positive or HBV DNA detectable) that are eligible for inclusion must be treated with antiviral therapy (per local institutional practice) prior to enrollment to ensure adequate viral suppression (HBV DNA <2000 IU/mL), must remain on antiviral therapy for the study duration, and continue therapy for 6 months after the last dose of investigational product(s)
14. At least one measurable lesion according to RECIST v1.1.
15. Adequate organ and marrow function, as defined below:
    - Hemoglobin ≥9 g/dL
    - Absolute neutrophil count ≥1,500/μL
    - Platelet count ≥75,000/μL
    - Total bilirubin ≤2.0 × ULN
    - ALT ≤3 × ULN
    - Albumin ≥2.8 g/dL
    - INR ≤1.6
    - Calculated creatinine clearance ≥45 mL/minute as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine creatinine clearance
16. Females of childbearing potential or non-sterilized male who are sexually active must use a highly effective method of contraception
17. Females of childbearing potential must have negative serum or urine pregnancy test

3.2 Exclusion Criteria

1. Prior invasive malignancy within 2 years except for noninvasive malignancies such as cervical carcinoma in situ, in situ prostate cancer, non-melanomatous carcinoma of the skin, lobular or ductal carcinoma in situ of the breast that has been surgically cured
2. Contraindicated of SBRT: Any one hepatocellular carcinoma >25 cm; Total maximal sum of hepatocellular carcinoma >30 cm; More than 3 discrete hepatic nodule; Direct tumor extension into the stomach, duodenum, small bowel, large bowel, common or main branch of biliary tree
3. Severe, active co-morbidity
4. Presence of extra-hepatic metastases (M1)
5. Vp4: presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both) or inferior vena cava (IVC) thrombosis or involvement
6. Presence of clinically meaningful ascites as ascites requiring non pharmacologic intervention (eg, paracentesis) or escalation in pharmacologic intervention to maintain symptomatic control
7. Hepatic encephalopathy
8. Active or untreated gastrointestinal varices

9. Untreated central nervous system (CNS) metastatic disease, lepto-meningeal disease, or cord compression
10. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
11. Prior treatment with any other anti-programmed cell death protein-1 (anti-PD-1), or PD Ligand-1 (PD-L1) or PD Ligand-2 (PD-L2) agent or an antibody targeting other immuno-regulatory receptors or mechanisms
12. Irritable bowel syndrome or other serious gastrointestinal chronic conditions associated with diarrhea within the past 3 years prior to the start of treatment
13. Known history of testing positive for HIV or known acquired immunodeficiency syndrome.
14. On chronic systemic steroid or any other forms of immunosuppressive medication within 14 days prior to the treatment. Except:
    (a) intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);
    (b) Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
    (c) Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
15. Active or prior documented autoimmune or inflammatory disorders in the past 2 years, except diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment
16. History of primary immunodeficiency or solid organ transplantation
17. Receipt of live, attenuated vaccine within 28 days prior to the study treatment
18. Active infection requiring systemic therapy
19. Severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb)
20. Females who are pregnant, lactating, or intend to become pregnant during their participation in the study
21. Psychiatric disorders and substance (drug/alcohol) abuse

4. STUDY SCHEMA



Protocol treatment must begin within 28 days after study registration

Patient Population (See section 3 for eligibility)

- Unsuitable for surgical resection or transplant or radiofrequency ablation (RFA)
- Barcelona Clinic Liver Cancer Stage (BCLC) Intermediate (B) or Advanced (C)
- No main portal vein thrombosis
- No lymph node nor extra-hepatic metastases

5. REGISTRATION PROCEDURE

5.1 Clinical Evaluation / Management

- Document performance status
- Documentation of liver disease etiology including cirrhosis, hepatitis history (hepatitis B and hepatitis C), alcohol, autoimmune disease, non-alcoholic steatohepatitis (NASH)
- Documentation of prior HCC therapies
- Initiation of treatment of viral hepatitis B (if untreated) prior to study therapy
- Patients with known portal hypertension or known history of varices are encouraged to have an endoscopic assessment of and appropriate treatment of varices within 6 months of study entry
- Blood tests including complete blood picture, liver function test, renal function test, free T4 and TSH, eGFR, clotting profile within 28 days prior to study entry
- Alpha-fetoprotein (AFP) within 28 days prior to study entry

- Urine or serum pregnancy test every 4 weeks while on avelumab therapy
- Free T4 and TSH must be performed at baseline and at least every 8 weeks during avelumab treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks)
- 20cc blood for bio-banking: Peripheral blood monocytic cells (PBMC) will be collected to analyze the peripheral T-cell response during treatment

5.2 Radiological Evaluation

All HCC patients are required to have a dynamic imaging with contrast (MRI) to confirm the diagnosis of HCC and assessment of tumor status

- Number of HCC nodule(s)
- Sum of maximum diameter of tumor(s)
- Degree of vascular involvement: inferior vena cava, main portal vein, right or left portal vein, peripheral portal branches, hepatic vein
- Extra-hepatic disease status, number of sites and sum of maximum diameter of extra-hepatic disease

MRI

MRI will be performed on 1.5T GE Signa system (GE Healthcare, Milwaukee, WI) or Philips 3T MRI Achieva scanner (Philips Healthcare, Best, The Netherlands) with a 12/16-channel, phased-array body coil. The protocol, as recommended by LI-RADS v2017 includes axial free-breathing fat-suppressed echo-planar imaging based DW-MRI, axial breath-hold fat-suppressed 2-dimensional (2D) fast spin-echo T2W with short and long echo times, axial breath-hold 2D in- and opposed-phase T1W and axial 3D gradient-echo T1W before and after contrast injection (arterial, portovenous and delayed phases).

The cross-sectional images will be reviewed by a multi-disciplinary team.

5.3 Quality-of-Life Evaluation

Quality of life will be assessed by the previously validated EORTC-QLQ-C30 and FACT-Hep questionnaire. The EORTC QLQ-C30 incorporates 30 items comprising five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. The FACT-Hep is a 45-item self-report instrument designed to measure health-related quality of life (HRQL) in patients. All forms will be self-administered surveys. A nurse or other health care provider will be available to help the patient with any questions regarding the QOL forms.

5.4 Informed Consent

The Investigator(s) (according to applicable regulatory requirements), or a person designated by the Investigator(s), and under the Investigator(s)'s responsibility, should fully inform the

patient of all pertinent aspects of the clinical study including the written information giving approval/favorable opinion by the Ethics Committee (IRB/EC). All participants shall be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patients' participation in the clinical study, the written Informed Consent Form (Form B) and any other local applicable documents in accordance with local laws and regulations, should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent From used by the Investigator(s) for obtaining the patient's informed consent must be reviewed and approved by the appropriate Ethics Committee (IRB/EC) for approval/favorable opinion.

During a patient's participation in the study, any updates to the consent form any updates to the written information will be provided to the patient.

Further information about the informed consent is available in Section 9.2 and Section 9.3.

5.5 Registration Guidelines

- All the patients must be registered with the Investigator(s) prior to initiation of treatment.
- Forms A (registration) and B (consent) will be submitted.
- The registration desk will confirm all eligibility criteria and obtain essential information (including patient number).

6. STUDY INTERVENTION

6.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator(s) to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational products is Avelumab for injection.

6.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational product.

6.3 TACE

6.3.1 Procedure

Procedure of TACE will be standardized. A femoral artery puncture will be performed under local anesthesia. Celiac and superior mesenteric arterial and porto-venogram will be done to delineate arterial anatomy, to exclude main portal vein occlusion and to define size and number of tumor nodules. The right or left hepatic artery will then be super-selectively catheterized. An emulsion of a mixture of cisplatin (1mg/ml) with lipiodol in a volume ratio of 1 to 1 will be prepared. A maximum of 60ml (equivalent to 30mg of cisplatin) mixture will be injected slowly under fluoroscopic monitoring. The amount of mixture used will depend on tumor size, number and arterial blood flow. The aim is to deliver a sufficient amount of emulsion to tumor without retrograde flow. In case of bi-lobed HCC or super-selective cannulation is not possible, the emulsion will be injected to hepatic artery proper that distal to origin of gastro-duodenal artery. This will be followed by embolization with gelfoam pellets of 1mm diameter mixed with 40mg of gentamicin.

6.3.2 TACE adverse event

Common (60-80%)

Post-embolization syndrome (RUQ pain, nausea, fatigue, fever, ileus and transient raised of liver enzymes), usually self-limiting and recover within 7-10 days

Uncommon side effects (<5%)

Hepatic decompensation, liver abscess, cholecystitis, bile duct injury, gastroduodenal ulceration and renal dysfunction

6.3.3 TACE Toxicity Assessment During Therapy

Patient should be seen at least once after TACE before initiation of SBRT. SBRT can be commenced if there is no grade 3 or 4 toxicity, bilirubin ≤3.0 mg/dL, Child Pugh score ≤7 and the treating physician recommends continuation. Otherwise, a delay in SBRT should occur until toxicities resolve.

6.4 SBRT

SBRT screening and planning will be performed by radiation therapists, medical physicists, and oncologists. Treatment will be delivered by a 6MV/10MV linear accelerator at 4 weeks (or within 21-35 days) after TACE

6.4.1 Immobilization and Simulation

Patients will be positioned supine in an Alpha Cradle or equivalent immobilization device will be custom made for each patient. Treatment planning CT scans will be required to define gross tumor volume (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.

Breath-hold CT or average phase CT (from 4D-CT) may be used as the baseline CT for radiation therapy planning. 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. Breathing motion management is recommended if breathing motion is >5 mm. Motion management can be addressed using respiratory gating, active breathing control (ABC), or abdominal compression.

6.4.2 Target volumes

Gross tumor volume (GTV) is defined as HCC focus that is visualized on contrast imaging, usually best seen on arterial phase (as hyperintensity) or washout out at portovenous/ delayed phase.

Clinical target volume (CTV) is defined as GTV with expansion to include the lipodol stained area.

Planning target volume (PTV) will provide margin around each CTV to compensate for respiratory motions. Individualized margin will be added to CTV to form the planning target volume (PTV) to compensate for respiratory motions. The margin recipe depends on the motion management solution utilized. Typically, a minimum PTV of 4mm around each CTV is required and the maximum permitted PTV is 20mm.

6.4.3 Dose Specifications

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.

Prescription Dose: 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 minimal planned prescription dose to PTVs is 27.5 Gy. 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. 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.

Dose Specification: The prescription isodose should encompass 95% of PTV. 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.

Vascular tumor thrombosis (e.g., portal vein thrombosis) dose should be the same as the HCC prescription dose. However, lower doses are acceptable if required to maintain normal tissue limits, since the cancer density may be lower than parenchymal HCC.

Dose prescription based on mean liver dose (MLD)

Prescription dose	Liver – GTV mean dose	
	Ideal	Acceptable
50Gy	≤13Gy	13-13.2Gy
45Gy	≤13Gy	15-15.2Gy
40Gy	≤15Gy	15-15.2Gy
35Gy	≤15.5Gy	15.5-15.7Gy
30Gy	≤16Gy	16-16.2Gy
27.5Gy	≤17Gy	17-17.2Gy

Organ-at-risk (OAR) dose constraints

Compliance Criteria:

	Ideal	Acceptable
Priority 1: Mandatory dose constraints		
Stomach, small intestine, duodenum: Max (to 0.5cc)	30Gy	>30Gy but ≤32Gy
Large bowel, oesophagus: Max (to 0.5cc)	32Gy	>32Gy but ≤34Gy
Spinal cord + 5mm: Max (to 0.5cc)	25Gy	>25Gy but ≤28Gy
Kidney: Bilateral mean dose	≤10Gy	>10Gy but ≤12Gy

Priority 2: Non-mandatory dose constraints	
Heart: Max (to 30cc)	<30Gy
Gall bladder: Max (to 0.5cc)	<55Gy
Common bile duct: Max (to 0.5cc)	<50Gy
Central biliary structure (main portal vein + 1.5cm):	V40 <21cc
Skin: Max (to 0.5cc) (external + 5mm)	<32Gy
Great vessel: Max (to 0.5cc)	<60Gy

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

(a) PTV dosimetry

- The intent is for prescription dose to cover 95% of each PTV
- The PTV should be treated to as high a dose as possible, respecting normal tissue constraints (as above)
- Modifying required PTVs due to close proximity of adjacent OARs is not permitted

Dose to 95% PTV	
Per Protocol	Prescription dose +/- 5%
Variation acceptable	90% - 110% of prescribed dose
Derivation unacceptable	<90% or >110% of prescribed dose, or <25Gy

6.4.4 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
- Skin irritation, itchiness, discomfort
- Transient changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

Less likely (<30%)

- Nausea, vomiting

- 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.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging

6.4.5 Radiotherapy Toxicity Assessment During Therapy

Patients will be assessed at least once during radiation therapy for toxicity. Radiation therapy will continue as planned as long as there is no grade 3 or 4 toxicity, bilirubin ≤3.0 mg/dL, Child Pugh score ≤7 and the treating physician recommends continuation. Otherwise, a delay in radiation therapy should occur with possible continuation of radiation after toxicities resolve. If the patient discontinues radiation therapy prematurely, the patient may be considered for study Avelumab, if the Child score is Child Pugh ≤7 and the treating physician recommends protocol treatment continuation.

6.4.6 Radiation Modification Table

TOXICITY	MODIFICATION
Hematological	
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 (nausea, vomiting and diarrhea)	
Grade 1 or 2	Continue radiation
Grade 3	Hold radiation until ≤ grade 2, then continue
Grade 4	Discontinue radiation
Hepatic dysfunction	
Grade 1 or 2 AST or ALT	Continue radiation
Grade 3 AST or ALT	Hold radiation until ≤ grade 2, then continue
Grade 4 AST or ALT	Hold radiation 1 week and until ≤ grade 2, then continue
Bilirubin ≤3.0 mg/dL	Continue radiation
Bilirubin >3.0 mg/dL	Hold radiation until improved ≤3.0, then continue

Child-Pugh score >7	Hold radiation until improves to CP score ≤7
Other non-hematological	
Grade 1 or 2	Continue radiation
Grade 3	Hold radiation until ≤ grade 2, then continue
Grade 4	Discontinue radiation

6.5 Checkpoint Inhibitor: Avelumab

Avelumab will be started 14 days (or 14-18 days) upon completion of SBRT.

6.5.1 Avelumab Dosage Form and Packaging

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and will be supplied by the manufacurer in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. Avelumab will be packed as IMP in boxes each containing 8 vials. The information on the study treatment will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2ºC to 8ºC) that is monitored with temperature control devices.

6.5.2 Avelumab Preparation

The contents of the avelumab vials are sterile and non-pyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard clean-up procedures for biologic products.

Avelumab must be diluted with 0.9% sodium chloride (normal saline solution). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided. Must use tubing with in line, low protein binding 0.2 micron filter made of polyether sulfone (PES) during administration.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for each dose to ensure they did not experience either a weight loss or gain of >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the avelumab dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

6.5.3 Avelumab Administration

Avelumab 10 mg/kg will be administered on Day 1 of each 2-week study cycle. Avelumab may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons.

Pre-medication: Avelumab will be administered as a 1-hour IV infusion. In order to mitigate infusion-related reactions, a premedication regimen of diphenhydramine 25 to 50 mg IV or oral equivalent and paracetamol 500 mg IV or oral equivalent is mandatory approximately 30 to 60 minutes prior to each dose of avelumab.

Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should beavailable for immediate access.

Observation period: Following infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

Drug accountability including receipt and return, local discard and destruction, if appropriate, must be completed with appropriate documentation for all study sites. Lot number, and expiry date for Avelumab is recorded in the study site as per local guidelines unless otherwise instructed by the Sponsor.

The investigator is responsible for taking steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

6.5.4 Avelumab Adverse Event

- Infusion related reaction
- Fatigue
- Immune-related adverse events include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia, rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

6.5.5 Dose Modifications for Avelumab as Single Agent

For avelumab, no dose reductions are permitted in this study, but doses may be omitted based on persisting toxicity. Any adverse event suspected to be immune related should be managed according to the guidance for management of irAEs (see the following tables).

6.5.6 Adverse Drug Reaction Requiring Avelumab Discontinuation or Delays

The following adverse reactions (ADRs) require permanent treatment discontinuation of avelumab:

Any Grade 4 ADRs require avelumab treatment discontinuation except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator(s), do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade 3 ADRs require avelumab treatment discontinuation except for any of the following:

- Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to Grade ≤1
- Single laboratory values out of normal range (excluding Grade ≥3 liver function test increase) that are unlikely related to trial treatment according to the Investigator(s), do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in Eastern Cooperative Oncology Group Performance Status (ECOG PS) to 3 that resolve to ≤2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is 3 on the day of trial drug administration).

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤1 within 2 weeks treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤1 within 2 weeks, avelumab should be held. If after another 2 weeks the event has not resolved to Grade 1, the patient should permanently discontinue treatment with an avelumab (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same patient, treatment with avelumab has to be permanently discontinued.

6.5.7 Management of Avelumab Infusion-Related Reaction

Since avelumab is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction

and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table.

Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 — mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 — moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 — severe or **life-threatening** Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study avelumab and must not receive any further avelumab treatment.
- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on Investigator(s)'s medical judgment. - If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = non-steroidal anti-inflammatory drugs.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after

implementation of the modifications indicated in Table 6 (including reducing the infusion rate by 50%), the Investigator(s) may consider treatment with corticosteroids, and the infusion should not be resumed. At the next dose, the Investigator(s) may consider the addition of H2 blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

Severe Hypersensitivity Reactions If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator(s) immediately.

Symptoms include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Patients should be placed on monitor immediately, and the intensive care unit (ICU) should be alerted for possible transfer if required.

6.5.8 Avelumab: Immune-Related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, avelumab may cause toxicity by increasing the immune response, leading to inflammatory reactions collectively referred to as immune-related adverse events (irAEs).

Immune-related adverse events described with this class of drugs include drugs include dermatitis, pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia, rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any adverse event which may have an underlying immune-mediated mechanism including those described above, and without other confirmed etiologies, should be considered immune-related and managed according to guidelines described in this section.

Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade):

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grades 1 to 2 (persistent): manage similar to high grade AE (Grades 3 to 4).
- Grades 3 to 4: treat with high dose corticosteroids.

For patients receiving avelumab alone, any event suspected to be immune-related should be managed according to the guidance for management of irAEs in this section and Table.

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade I : Resume avelumab therapy If persists >5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists >1 to 2 weeks or recurs: Withhold avelumab therapy

		Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids

	Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT >3.0 × ULN and/or Total bilirubin > ULN to 1.5 × ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 AST or ALT >3.0 to 5 × ULN and/or Total bilirubin >1.5 to 3 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤1 : Resume routine monitoring; resume avelumab therapy. If elevation persists >5 to 7 days or worsens: Treat as Grade 3 to 4.

Grade 3 to 4 AST or ALT >5 × ULN and/or total bilirubin >3 × ULN	Permanently discontinue therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 × ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine Increased >1.5 and ≤6 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased >6 × ULN	Permanently discontinue avelumab therapy Monitor creatinine daily	If returns to Grade ≤1: Taper steroids over at least 1 month.

	1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult*. Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult*. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

*Local guidelines, or eg. ESC or AHA guidelines

ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines

AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 **(hypothyroidism,** **hyperthyroidism, adrenal** **insufficiency, type I diabetes** **mellitus)**	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies **(hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)**	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression) . Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs **(NCI-CTCAE v4)**	**Initial Management**	**Follow-up Management**

Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency	Permanently discontinue avelumab therapy Specialty consult	

Persistent Grade 2 or 3 irAE lasting 12 weeks or longer		

6.6 Record of Treatment Details and Acute Reactions (Form C)

The treatment details of TACE, SBRT and Avelumab will be documented. The incidence of acute toxicities ≥ grade 3 by Common Toxicity Criteria for Adverse Events version 4.0 (CTCAE-v4) will also be recorded.

7. FOLLOW UP AND OUTCOME EVALUATION

7.1 Follow-Up Schedule

All participants will be followed every 2 weeks during the intervention. At each visit, patient's performance status and toxicity of treatment will be monitored, and blood test will be checked for complete blood picture, liver function, renal function, clotting profile and alpha-fetoprotein (AFP). A urine or serum pregnancy test needs to be performed at least every month while the subject is on avelumab therapy. Free T4 and TSH must be performed at least every 8 weeks during avelumab treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks). Upon completion of intervention, patients will be seen at least every 4 months in the first two years, and then every 6 months.

Blood-borne immune markers will be checked every 4 weeks for the first 24 weeks.

Extended safety follow-up:

- *Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration.*
- *The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.*

Treatment response and operability will be evaluated by contrast CT or MRI every 3 months during treatment, every 4 months in the first and second year after treatment, then every 6 months. All CT or MRI reporting will be according to Modified Response Evaluation Criteria for Solid Tumours (mRECIST) criteria.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30) and Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaires will be used for assessment of quality of life every 3 months in the first two years, then every 6 months.

7.2 Decision on Resectability, Subsequent Treatment and Treatment Failure

A multidisciplinary meeting consists of surgeons, oncologists, and radiologists will be held every 3 months to evaluate treatment response/failure, to decide on subsequent treatment.

Successful downstage and disease control (as defined by complete response, partial response and stable disease) will be evaluated for resection or transplantation of HCC

UCSF Criteria will be used to determine the suitability of transplantation

- Single tumor ≤6.5cm
- Or up to 3 tumors ≤4.5cm, and total sum is 8cm
- No vascular invasion

Treatment failure can be due to either poor liver function or tumor progression

Poor liver function is defined as

- Hepatic encephalopathy,
- Diuretic refractory ascites,
- Variceal bleeding,
- Bilirubin >50umol/L,
- Prothrombin time >4sec, or
- Child Pugh C status.

Tumor progression is defined as

- Extra-hepatic disease,
- New onset major vascular invasion (portal vein or hepatic vein invasion),
- Progressive disease according to mRECIST,

In patients who have treatment failure, unacceptable toxicity, or they have reached the end of treatment. Subsequent treatment will be decided in multidisciplinary panel based on best interests of patients. There is no restriction on choice of subsequent treatment.

7.3 Outcome Measures

7.3.1 Primary Endpoint

- Number of patients amenable to curative surgical interventions is defined as number of patients receiving curative surgical resection or transplantation after successful down-sizing of tumor(s) by intervention

7.3.2 Secondary Endpoints

- Response rate measured by mRECIST criteria:

  Complete response (CR): Disappearance of any intra-tumoral arterial enhancement in all target lesions

  Partial response (PR): At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions

  Stable disease (SD): Any cases that do not qualify for either partial response or progressive disease

  Progressive disease (PD): An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

- Number of patients amenale to curative surgical interventions and/or achieve radiological complete response: defined as number of patients receiving curative surgical intervention or transplantation after successful downstaging (i.e. equivalent to primary endpoint) plus number of patients achieveing radiological CR per mRECIST criteria. This endpoint is to reflect the number of patients achieve complete tumor clearance and potentially cure.
- Time to progression (TTP): measured from the date of first study treatment to radiographically documented progression according to mRECIST 1.1. This does not include death from any cause.
- Progression-free survival (PFS): measured from the date of first study treatment to radiographically documented progression according to mRECIST 1.1 or death from any cause (whichever occurs first). Participants alive and without disease progression or lost to follow-up will be censored at the date of their last radiographic assessment.
- Overall survival (OS): measured from date of first study treatment to the date of death from any cause. Participants alive or lost to follow-up will be censored at the date of their last visit.
- Quality of life (QoL): as assessed by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) questionnaires
- Safety outcome measures: Incidence, nature, and severity of adverse events graded according to the United States National Cancer Institute The Common Terminology Criteria for Adverse Events (NCI CTCAE 4.0)
- Pathological response: assessed as the percentage of surface with non-viable cancer cells (represented by necrosis or fibrosis, the ultimate stage of necrosis) in relation to the total tumor area and will be equal to: 100% – viable cancer cells (%). If there are

multiple tumors, the mean percentage will be used. Pathological complete response (pCR) is defined by the absence of viable tumor cells in any nodule.

- Disease control rate: Percentage of patients that had a CR, PR, or stable disease (SD) ≥ 6 months per mRECIST
- Local control: defined as absence of recurrence within the high-dose region (80% isodose volume), demonstrated by new enhancement or mRECIST progressive disease
- Duration of response: time from first documented evidence of CR or PR until the first documented sign of disease progression (PD) or death from any caus
- Pattern of failure:
  (1) In-field failure: defined as recurrence within the high-dose region (80% iso-dose volume), demonstrated by new enhancement or mRECIST progressive disease.
  (2) Out-field (intra-hepatic): defined as new or mRECIST progressive disease within liver parenchyma, but outside the SBRT treated volume
  (3) New vascular invasion: defined as new portal or hepatic vein invasion
  (4) Distant failure: defined as new disease outside liver parenchyma
- Radiological response per RECIST 1.1

7.4 Follow-Up and Record of Events (Form D)

- The patient should be followed-up until death.
- The dates of diagnosis of in-field, out-of-field (intra-hepatic), and distant failure should be recorded.
  - In-field failure: defined as recurrence within the high-dose region (80% iso-dose volume), demonstrated by new enhancement or mRECIST progressive disease.
  - Out-field (intra-hepatic): defined as new or mRECIST progressive disease within liver parenchyma, but outside the SBRT treated volume
  - Distant failure: defined as new disease outside liver parenchyma
- The incidence of late toxicities ≥ grade 3 by Common Toxicity Criteria for Adverse Events version 4.0 (CTCAE-v4) should be recorded.
- All causes of death (if occur) will be recorded. Deaths due to unknown cause are counted as deaths due to HCC if disease is still present at last assessment.

7.5 Criteria for Removal From Protocol Treatment

- Disease progression
- Inter-current disease that would affect assessments of clinical status to a significant degree, require discontinuation of drug, or both
- Unacceptable toxicity
- The patient may withdraw from treatment at any time for any reason. The reason should be recorded. Follow-up will be continued for all consenting patients per standard clinical procedures, including regular follow-up visits, clinical and laboratory assessments for up to 5 years

- Avelumab treatment for maximum of 2 years

7.6 Exploratory Biomarkers

- **Blood Borne Immune Panel Exploratory Analysis**

  Peripheral blood monocytic cells (PBMC) will be collected at baseline, then every 4 weeks after initiation of treatment for 20 weeks.

  Procedure: after collection of patients' blood, the sample will be centrifuged for 15 min at 3000 rpm. After removal of the plasma, PBMC will be isolated either by Ficoll-paque or red cell lysis buffer. The isolated PBMC will be washed twice with PBS for immediate analysis or frozen for further investigation. For the phenotyping of the immune cells, PBMC will be stained with different antibodies and examined by flow cytometry. The identification of CD8+ and CD4+ T cells are defined as CD8+ CCR7+ CD45RA+ and CD4+ CCR7+ CD45RA+, respectively. For the T-reg cell, we define as positive for CD4 and Foxp3. We will also examine the expression of Ki-67 and TIM-3 in the T-cells to demonstrate the possible cell proliferation and functions. We will also examine the expression of PD-1 and PD-L1 expression on each subset of cell to correlate the pathological response and clinical outcome.

- **Tumor samples (immune-related markers in surgical specimens)**

  The expression and spatial distribution of immune-related or response-related markers by immunohistochemistry may also include, but may not be limited to, PD-L1, CTLA-4, CD3, CD4, CD8, CD45RO, forkhead box P3, granzyme B, OX40, PD1, cleaved caspase 3 and Ki67.

7.7 Safety Reporting

7.7.1 Adverse Events (AE)

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

7.7.2 Serious Adverse events (SAE)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the Investigator(s), places the patient at immediate risk of death)
- This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the Investigator(s)'s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are <u>not</u> synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded in the clinical database.

7.7.3 Adverse Events of Special Interest (AESI)

AESIs (serious or non-serious) are a subset of Events to Monitor of scientific and medical concern specific to the Merck Drugs in this protocol for which ongoing monitoring and rapid communication by the Investigator(s) to Merck Drug Safety is required. Such an event might require further investigation in order to characterize and understand it.

Infusion related reactions including study intervention hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis) have been identified as adverse events of special interest for avelumab.

Any AE that is suspicious to be a potential immune-mediated adverse reaction or infusion related reaction will be considered an AESI. AESIs do not require expedited reporting unless

they are serious. Should the AESI be serious, a SAE form should be filled instead and the reporting process for SAEs should be followed.

7.7.4 Pregnancy Reports

Female patients of childbearing potential will be instructed to immediately inform the Investigator(s) if they become pregnant during the study.

7.7.5 Assessment of Causality of Adverse Events

Investigator(s) should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "Yes" or "No" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

7.7.6 Methods of Recording Adverse Events

All AEs must be documented in the appropriate section of the CRF. An SAE report form (initial or follow up) must be completed in addition.

The following aspects must be recorded for each event in the CRF:

A description of the AE in medical terms, not as reported by the subject;

- The date of onset (start date)
- The time of onset (start time)
- The date of recovery (stop date)
- The time of recovery (stop time)
- The severity of the sign and/or symptom or clinically significant abnormal laboratory value according to NCI-CTC, Version 4.0. If no toxicity grade is described for a given sign, symptom or abnormal laboratory value, the Investigator(s) will grade the severity as mid (grade 1), moderate (grade 2), severe (grade 3), or life-threatening or disabling (grade 4).

- Death (grade 5) as defined by NCI-CTCAE v.4.0 is mainly regarded as an outcome and will be documented accordingly (see below).
- The causal relationship to Avelumab, TACE and radiotherapy as assessed by the Investigator(s); the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study drug or study procedures are to be used:
  - Not Related = not suspected to be reasonably related to the investigational product. AE could not medically (pharmacologically/ clinically) be attributed to the investigational product under study in this protocol
  - Related = suspected to be reasonably related to the investigational product. AE could medically (pharmacologically/ clinically) be attributed to the investigational product under study in this protocol
- Action taken on Avelumab (none, medication discontinued, dose reduction, medication delayed, reduction of infusion rate).
- Other action (none, concomitant medication given, new or prolonged hospitalization, procedural surgery).
- The outcome according to the following definitions:
  - Recovered without sequelae (AE disappeared)
  - Recovered with sequelae (AE has resulted in permanent disability/incapacity)
  - Not yet recovered
  - Not recovered at death
  - Change in toxicity grade/severity or seriousness (e.g., an AE with no change of toxicity grade but newly classified as an SAE due to hospitalization.
  - Fatal (AE resulted in death)
- Concomitant medication given: Yes or No (Note: If this question is answered "Yes" the corresponding serious criteria must be ticked)
  - Subject died
  - Life-threatening
  - New or prolonged hospitalization
  - Persistent/significant disability
  - Congenital abnormality
  - Important medical event
  - Seriousness: Yes or No

If in any one patient the same AE occurs on several occasions, then the AE in question must be documented and assessed anew each time.

7.7.7 Procedure of Reporting Serious Adverse Events

The Sponsor-Investigator(s) primary responsibilities for safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and Merck, as required by local regulations (for regulatory reporting) and as required by the ISS agreement (for reporting to Merck).

The following reportable events must be submitted to Merck within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The Principal Investigator(s) will assume responsibility for submitting the reportable event(s) to Merck as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events (see section 7.4.2)
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Contact information for submission of reportable events to Merck:

Fax: +49 6151 72 6914 or

E-mail: ICSR_CT_GPS @merckgroup.com

Specifying:

- PROTOCOL Number and/or Title
- Funder's Study Identifier
- SUBJECT Number
- Principal Investigator Name
- Sponsor Name
- SAE/ONSET DATE

7.7.8 Monitoring of subjects with Adverse Events

Any AE that occurs in the course of a clinical study must be monitored and followed up until the last study visit. It is the responsibility of the Investigator(s) that any necessary additional therapeutic measures and follow-up procedures are performed.

8. STATISTICS

8.1 Statistical Analysis

- Patients who complete TACE will be considered as the study population for primary and secondary endpoints.
- The primary endpoint - the rate of patients amendable to curative surgical intervention will be estimated based on exact binomial distribution.

- Objective response rate (ORR), pathological response rate, and number of patients amendable to curative interventions and / or radiological CR will be expressed based on exact binomial distribution.
- Survival outcomes, including TTP, PFS and OS and their corresponding 95% confidence interval, will be estimated using Kaplan-Meier method.
- Patient reported QoL scores will be estimated at baseline, during and following therapy. Scores at each time point will be summarized with descriptive statistics including means, standard deviations, median and range. The changes from baseline during therapy and after therapy will be calculated for each patient and also summarized with means and standard deviations/95% CI. Linear mixed-effect model will be used to study the longitudinal changes of QoL scores.
- All of the tests and reported P values will be 2-tailed, and $P<0.05$ will be considered statistically significant. The analyses will be performed using statistical software packages SPSS and R.

Procedures for Handling Missing, Unused, and Spurious Data: All available data will be included in the data listings and tabulations. Where appropriate, imputations of values for missing data for primary and secondary efficacy analyses will be performed as specified in the Statistical Analysis Plan. All data recorded on the CRF will be included in the data listings that will accompany the clinical study report.

If, after the study has begun, but prior to the conduct of any analysis, changes made to primary and / or key secondary endpoints, or the statistical methods related to those hypotheses, then the protocol will be amended. Changes to exploratory analyses made after the protocol finalized will be documented and referenced in the final report. Post hoc exploratory analyses will also be identified in the final report.

8.2 Sample Size Calculation

H0: The null hypotheses of no difference in the number of patients who can undergo surgery: similar to the historical result of QMH, 5% of patients can undergo surgical intervention after TACE.

H1: The alternative hypotheses of treatment efficacy: the experimental treatment would result in 20% of study population who can undergo surgical resection after treatment response.

To detect 15% of differences from 5% to 20% in the number of patients proceeding to surgery, with Type I error of 0.05 and 80% power, assume 10% patients who have withdrawnmay withdraw consent and patients who cannot be contacted during survival follow-up period, withdrawn subjects are only tobefore starting their protocol treatment. Patients will not be replaced once their protocol treatment started. The target accrual is 33 patients. Simon's two-stage optimal design will be used. In the first stage ten patients will be enrolled. If at least one is amenable to curative surgical intervention, the study can proceed to the second stage and an

additional 19 patients could be recruited. If at least 4 of the total 29 patients are amenable to curative surgical intervention, the treatment will be considered worthy of further investigation.

8.3 Early Stopping Rule

Excessive toxicity will be monitored, which includes: (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 TACE, SBRT, or Avelumab alone, the increase to a rate of 30% or greater in the studied treatment will be considered unacceptable, and the study will be stopped prematurely. Upon the recruitment of these 33 patients, if 14 or more patients had treatment-related SAE, the study will be stopped. The corresponding lower bound of exact one-sided 90% confidence interval is 30.5%. The table below shows the stopping guideline scenarios for the first 8, 16 and 24 patients. For example, the study will be stopped when 11 of the first 24 patients develop an acute toxicity. The upper bound for the confidence intervals is 100%.

Number of patients with serious adverse event	Number of patients enrolled	Lower bound of exact one-sided 90% confidence interval
5	8	34.46%
8	16	31.78%
11	24	31.48%

9. ETHICAL, REGULATORY & STUDY OVERSIGHT CONSIDERATIONS

9.1 Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the clinical study in accordance with this clinical study protocol, ICH guideline for Good Clinical Practice (GCP) (ICH E6 R2 Step 4) approved on November 9, 2016) and applicable regulatory requirements in Hong Kong. These documents state that the informed consent of the subjects is an essential precondition for participation in the clinical study.

9.2 Subject Information

An unconditional prerequisite for a patient participating in the study is his/her written informed consent. Adequate information must therefore be given to the subject by the Investigator(s) before informed consent is obtained. A person designated by the Investigator(s) may give the information, if permitted by local regulations. A subject information sheet in the local language and prepared in accordance with Good Clinical Practice will be provided by the Investigator(s) for the purpose of obtaining informed consent. In addition to this written information, the Investigator(s) or his/her/their designate will inform the subject verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

The patient information sheet will be revised whenever important new information becomes available that may be relevant to the consent of patients.

9.3 Informed Consent (Form B)

The consent of the patient to participate in the clinical study has to be given in writing before any study-related activities are carried out. It must be signed and personally dated by the patient and by the Investigator(s)/person designated by the Investigator(s) to conduct the informed consent discussion.

Provision of consent will be confirmed in the case report form (CRF) by the Investigator(s). The signed and dated declaration of informed consent will remain at the Investigator(s)'s site and must be safely archived by the Investigator(s) so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the patient prior to participation.

If the patient or legally acceptable representative is unable to read, a reliable, independent and impartial witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject’s right to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative verbally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

9.4 Compensation to Subjects

The patients do not receive payment for taking part in the study. Patients who are entitled to discounted or free health care, e.g. civil servants, will receive their entitled free treatment as normal. The study is covered by an insurance policy from the Clinical Trial Center of the

University of Hong Kong, in which to cover claim by, or compensation for, patients treated in study, e.g. those who developed AEs or SAEs, and this will be covered by the existing hospital insurance.

9.5 Ethics Committee or Institutional Review Board

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, IB) to the IRB/EC for their favourable opinion. The favourable opinion/approval of the IRB/EC will be filed in the study file. The study will only commence following provision of a written favourable opinion.

Any amendments to the protocol will be submitted to the IRB/EC and they will be informed about SAEs in accordance with national and/or local requirements.

9.6 Role of Funding Source

The study drug and partial funding will be provided by Merck KGaA, Darmstadt, Germany. The Funder otherwise has no role in study design, data collection, data analysis, data interpretation, or in the writing of the study report. The Funder will be review the manuscript before submission for publication.

9.7 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice.

The Sponsor agrees to submit all manuscripts or abstracts to the Funder for review before submission for publication. This allows the Funder to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10. STUDY MANAGEMENT

10.1 Data Quality Assurance

The main objective is to obtain those data required by the study protocol in a complete, accurate, legible and timely fashion. The data in the eCRF should be consistent with the relevant source documents.

The CRFs must be filled in completely and legibly (with either black or blue ballpoint pen, acceptable for use on official documents). Any amendments and corrections necessary must be undertaken and countersigned by the Investigator(s), stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids (e.g., Tipp-Ex®). The Investigator(s) must state his/her reasons for the correction of important data. In the case of missing data/remarks, the entry spaces provided in the case report form should be cancelled out so as to avoid unnecessary follow-up inquiries.

CRF entries will be done by the study team and checked against source documents, except for the pre-identified source data directly recorded in the CRF. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/EC), and the regulatory authorities to have direct access to source data which support the data on the CRF. Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

10.2 Direct Access to Source Data/Documents

For the purpose of ensuring compliance with the clinical study protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator(s) shall permit auditing by the Sponsor, the Funder, and inspection by applicable regulatory authority.

The Investigator(s) agree(s) to allow the auditors/inspectors to have direct access to the study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose personal identity or personal medical information.

The Investigator(s) will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator(s) is/are notified of a future inspection by the authority, he will inform the Sponsor.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authority will be communicated by the Investigator(s) to the Sponsor and the Funder as per timeframe stipulated in the ISS agreement.

The Investigator(s) shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

10.3 Study File and Archiving

The Investigator(s) shall maintain a Study File for the study purpose. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study in accordance with the local relevant regulations.

11. REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al.: Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
2. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology. 2005;42:1208-1236.
3. Lo C, Ngan H, Tso W, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35(5):1164-71.
4. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734-9.
5. Shim SJ, Seong J, Han KH, et al.: Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma. Liver international 2005;25:1189–1196.
6. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul 24;359(4):378-90.
7. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009 Jan;10(1):25-34.
8. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol. 1995;34(6):861-70.
9. Cárdenes H, Price T, Perkins S, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol. 2010;12(3):218-25.
10. Andolino D, Johnson C, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2011;81(4):e447-53.
11. Kang J, Kim M, Cho C, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. Cancer. 2012;118(21):5424-31.
12. Bujold A, Massey C, Kim J, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;31(13):1631-9.
13. Radiation Therapy Oncology Group RTOG 1112 protocol. Available from: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1112.
14. Huo YR, Eslick GD, et al. Transcatheter Arterial Chemoembolization Plus Radiotherapy Compared With Chemoembolization Alone for Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. JAMA Oncol. 2015 Sep;1(6):756-65.
15. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: from palliation to cure. Cancer. 2006;106(8):1653-1663.
16. Aguirre-Ghiso JA. Models, mechanisms and clinical evidence for cancer dormancy. Nat Rev Cancer. 2007;7(11):834-846.

17. Steel GG, Peckham MJ. Exploitable mechanisms in combined radiotherapychemotherapy: the concept of additivity. Int J Radiat Oncol Biol Phys. 1979;5(1):85-91.
18. Seong J, Kim SH, Suh CO. Enhancement of tumor radioresponse by combined chemotherapy in murine hepatocarcinoma. J Gastroenterol Hepatol. 2001;16(8):883-889.
19. Chan MK, Lee V, Chiang CL, Lee FA, Law G, Sin NY, Siu KL, Wong FC, Tung SY, Luk H, Blanck O. Lipiodol versus Diaphragm in 4D-CBCT-guided Stereotactic Radiotherapy of Hepatocellular Carcinoma. Strahlentherapie und Onkologie. Feb 2016, 192(2): 92-101
20. CL Chiang, AS Lee, KK Choi, et al. Stereotactic Body Radiation Therapy (SBRT) Combined With Transarterial Chemoembolization (TACE) in BCLC Stage B and C Hepatocellular Carcinoma (HCC). Int J Radiat Oncol Biol Phys. 2016 Oct; 96(2): Supplement: E162
21. Yoon SM, Ryoo BY, Lee SJ, et al. Efficacy and Safety of Transarterial Chemoembolization Plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinoma With Macroscopic Vascular Invasion: A Randomized Clinical Trial. JAMA Oncol. 2018 Mar 15.
22. Thomson AW, Knolle PA. Antigen-presenting cell function in the tolerogenic liver environment. Nat Rev Immunol. 2010 Nov;10(11):753-66.
23. Gehring AJ, Ho ZZ, Tan AT, et al. Profile of tumor antigen-specific CD8 T cells in patients with hepatitis B virus-related hepatocellular carcinoma. Gastroenterology. 2009 Aug;137(2):682-90.
24. Sandro B, Gomez-Martin C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol. 2013 Jul;59(1):81-8.
25. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 Jun 24;389(10088):2492-2502.
26. Bernstein MB, Krishnan S, Hodge JW, et al. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol. 2016 Aug;13(8):516-24.
27. Demaria S, Kawashima N, Yang AM, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin Cancer Res. 2005 Jan 15;11(2 Pt 1):728-34.
28. Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res. 2009 Sep 1;15(17):5379-88.
29. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med. 2012 Mar 8;366(10):925-31.
30. Golden EB, Demaria S, Schiff PB, et al. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res. 2013 Dec;1(6):365-72.
31. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Nov 16;377(20):1919-1929.
32. Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer. 2. Tokyo: Kanehara & Co., Ltd; 2003.

33. Yao FY, Ferrell L, Bass NM et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001;33(6):1394.
34. Investigator's Brochure Version 10 (29 May 2020) Avelumab (MSB0010718C)