Protocol ID: PEMRAD
Protocol Version/ Date: Initial / 11Apr2017
Amendment #1 / 01-May-2018
Amendment #2 / 06-Nov-2019
Amendment #3 / 20-Nov-2020
Amendment #4 / 09-Sep-2021

TITLE: Pembrolizumab and Stereotactic Radiotherapy Combined in Subjects with Advanced Hepatocellular Carcinoma – A Phase II Study (PEMRAD)

Coordinating Center:
Princess Margaret Cancer Centre
610 University Avenue
Toronto, ON M5G 2M9
Canada

Sponsor-Investigator:
Jennifer J Knox
Princess Margaret Cancer Centre
610 University Avenue
Toronto, ON M5G 2M9
Canada
Phone: +1-416-946-2399
Fax: 416-946-6546
Email: jennifer.knox@uhn.ca

Radiation Oncology Lead:
Laura A Dawson
Princess Margaret Cancer Centre
610 University Avenue
Toronto, ON M5G 2M9
Canada
Phone: +1-416-946-4501
Email: laura.dawson@rmp.uhn.on.ca

Hepatology Lead:
David K Wong
Princess Margaret Cancer Centre
610 University Avenue
Toronto, ON M5G 2M9
Canada
Email:dave.wong@uhn.ca

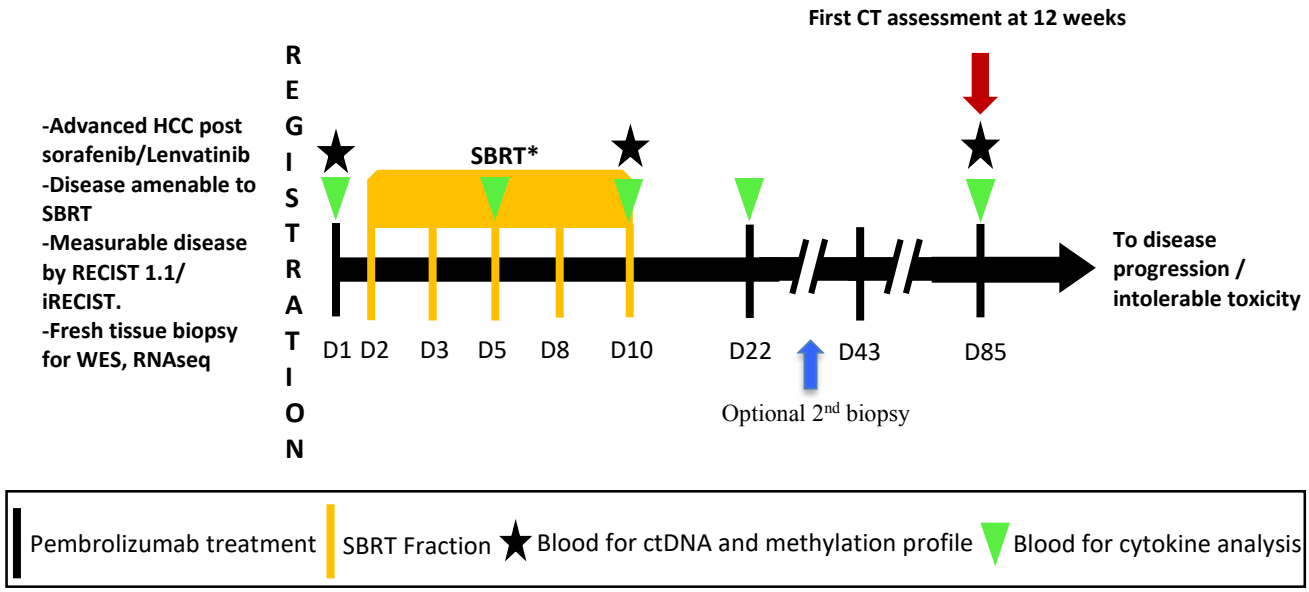
Participating Institutions:
Princess Margaret Cancer Centre
610 University Avenue
Toronto, ON M5G 2M9
Canada

Statistician:
Lisa Wang
Department of Biostatistics
Princess Margaret Cancer Centre
610 University Ave
Toronto, ON M5G 2M9
Phone: 416-946-4501 ext. 4883
Fax: 416-946-2048
lisawang@uhnres.utoronto.ca

Central Office Coordinator:
Nitika Solanki
Drug Development Program
Princess Margaret Cancer Centre
700 University Ave
Toronto, ON M5G 1X6
Phone: 416-946-4501 ext. 2630
Fax: 416-946-2016
nitika.solanki@uhn.ca

Investigational Agent: Pembrolizumab

SCHEMA



***SBRT will be given daily or every 2nd day on weekdays, and therefore cycle days may not correspond. Schema is for illustration purposes only. All treatment dates +/- 1 day.**

SYNOPSIS

Title of study:

Pembrolizumab and Stereotactic Radiotherapy Combined in Subjects with Advanced Hepatocellular Carcinoma – A Phase II Study (PEMRAD)

Objectives:

Primary:

- To assess the efficacy of combined SBRT and pembrolizumab in subjects with advanced hepatocellular carcinoma (HCC), by measurement of overall response rate (ORR).

Secondary:

- To assess response rate outside irradiated volumes (abscopal effect)
- Analyze response kinetics
- Determine progression-free and overall survival
- Assess safety of combined SBRT and pembrolizumab.

Exploratory:

- To explore predictors of response to combined SBRT and pembrolizumab in HCC, including molecular and imaging biomarkers associated with response outside irradiated volumes.

Study Design:

Single-arm, non-comparative, open-label phase II clinical trial of pembrolizumab with SBRT delivered during first cycle of systemic therapy.

Number of subjects:

The trial will follow a 2-stage design. During the first stage, 10 evaluable subjects will be enrolled. If 2 or more subjects demonstrate a response, the trial will continue to a total enrollment of 22 evaluable subjects. We expect to accrue up to 27 patients as some of the subjects may not be evaluable.

Main criteria for Inclusion/Exclusion:

1. Histologically- or cytologically-confirmed HCC, unsuitable for locoregional therapy (such as TACE, RFA), surgical resection or liver transplantation (BCLC stage B or C), with measurable disease by RECIST 1.1/iRECIST.
2. Disease progression after at least 8 weeks of sorafenib or lenvatinib, or discontinuation of sorafenib/lenvatinib due to intolerance with subsequent disease progression.
3. Tumor that is amenable to biopsy for correlative studies at time of study

registration, no contraindication to biopsy, and subject willing to undergo biopsy. In addition, the subject must consent to give blood for correlative studies, and have no contraindications to this.

4. Adequate liver function: Child-Pugh A5/6, ALT&AST ≤ 5 x upper limit of normal (ULN), bilirubin ≤ 34 umol/L, albumin ≥ 25 g/L.
5. ECOG Performance Status 0-1.
6. Intrahepatic HCC must be suitable for stereotactic radiotherapy – max 10 lesions to be treated, and total tumor diameter <20 cm. Smaller satellites of HCC or non-definite HCC need not be encompassed within SBRT volumes if needed to respect normal tissue limits.
7. No prior invasive malignancy, unless treated with curative intent and disease-free for 2 years prior to study entry.
8. Subjects with fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma-HCC are excluded.
9. Subjects with previous liver transplantation will be excluded.
10. Subjects with prior upper abdominal radiation therapy within planned volumes (exceeding standard tolerances) will be excluded.
11. Liver tumors must not invade main branch bile ducts or extend into adjacent organs.
12. Individual liver tumors must not measure >15cm in diameter
13. Subjects with contraindications to checkpoint inhibiting immunotherapy will be excluded: chronic autoimmune disease, immunosuppressive medications or corticosteroids (>10mg/day prednisone), HIV infection, or live/live-attenuatedvaccine (within prior 30 days).
14. Subjects with brain metastases will be excluded.
15. No previous cancer immunotherapy.
16. Subjects with alcohol related or non-alcoholic steatohepatitis (NASH) related cirrhosis will be excluded.
17. Subjects with a history of significant, active or unstable heart disease will be excluded.

Intervention:
Pembrolizumab will be administered intravenously as a 30-minute infusion at a dose of 200 mg every 21 days, until disease progression or intolerable toxicity.
Stereotactic radiotherapy will commence on day 2 of the first cycle of pembrolizumab, and will be delivered in 5 fractions over 5-15 days in accordance with institutional protocol, with a preferred schedule of beginning on a Tuesday, if Day 1 is on a Monday.

Correlatives:
A pre-treatment biopsy will be mandatory. Up to four good core biopsies will be obtained if deemed safe by radiologist performing the procedure. These will be banked for planned whole exome sequencing, gene expression profiling by RNAseq and DNA methylation mapping. Immunohistochemical analysis of PD-L1and tumour infiltrating lymphocytes will also be evaluated.

Patients deemed eligible will be presented with the consent to have an optional tumour

biopsy will be performed at 3-6 weeks on study. Whole blood will be drawn on cycle 1, Day 1 and Day 10 and Cycle 5 Day 1 for ctDNA analysis and DNA methylation profiling. These markers will also be analyzed at time of progression where possible. Blood will also be collected for peripheral cytokine analysis by electrochemiluminescence at Cycle 1, Day 1, Day 5, and Day 10, Cycle 3 Day 1, Cycle 5 Day 1 and at progression. Baseline diagnostic imaging and radiation planning imaging will be archived for future exploratory analyses, which will explore patterns of enhancement and change in responding patients compared with non-responders.
Statistics: The primary objective of the study is to assess the ORR of the combination of SBRT and pembrolizumab, as measured by RECIST 1.1. /iRECIST. Given the preliminary results with nivolumab, we would predict pembrolizumab alone to produce an ORR of approximately 15%. We hypothesize that combining pembrolizumab with SBRT will increase the ORR to 40%, a clinically meaningful increase in systemic response rate and indicative of significant activity. With 90% power, we would need to accrue 22 subjects in a two-stage study design, with a one-sided significance level of 10%. If 2 or more subjects show response from the first 10, we will continue to accrue to a total of 27, as we expect that some subjects will not be evaluable for the primary endpoint. A total number of 6 or more responders in 22 evaluable subjects would be considered to reject the null hypothesis. Response will be defined as best response at any time on study treatment. Secondary analyses will be performed without pre-specified assumptions of efficacy, given the lack of data in this setting.

LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	Alpha Fetoprotein
BCLC	Barcelona Clinic for Liver Cancer (staging)
BP	Blood Pressure
CBC	Complete Blood Count
CI	Confidence Interval
CP	Child-Pugh (Score)
CR	Complete Response
CT	Computed Tomogram
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
DDP	Drug Development Program
DRESS	Drug Rash with Eosinophilia and Systemic Symptom
cfDNA	Cell-free DNA
ctDNA	Circulating Tumor DNA
ECOG	Eastern Co-operative Oncology Group
GCP	Good Clinical Practice
GTV	Gross Tumour Volume
Gy	Gray
HCC	Hepatocellular Carcinoma
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
ICH	International Conference on Harmonization
irAE	Immune Related Adverse Event
iRECIST	immune related modified RECIST 1.1
IRB	Institutional Review Board
LFT	Liver Function Tests
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NE	Not Evaluable
NK	Natural Killer
NTCP	Normal Tissue Complication Probability
OAR	Organs at Risk
ORR	Overall Response Rate
OS	Overall Survival
OTN	Ontario Telemedicine Network
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Death-1
PDL-1	Programmed Death Ligand-1
PFS	Progression Free Survival
PTV	Planning target volume

PM	Princess Margaret Cancer Centre
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumor
REB	Research Ethics Board
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SD	Stable Disease
SJS	Stevens-Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
UHN	University Health Network
ULN	Upper Limit of Normal
US	Ultrasound
WES	Whole Exome Sequencing
RNAseq	RNA sequencing

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

To assess the systemic efficacy of combined SBRT and pembrolizumab in subjects with advanced HCC who have experienced disease progression after sorafenib or lenvatinib therapy, as measured by overall response rate (ORR). Both RECIST 1.1 and iRECIST (Seymour 2017) will be used. In addition, this study will look at the composite sum of irradiated tumor and other measurable metastatic disease as assessed by the following: local radiotherapy response, systemic pembrolizumab response and potential abscopal effect on all measurable disease.

1.2 Secondary Objectives

1. To assess the radiographic response rate in non-irradiated tumor lesions, following the combination treatment of pembrolizumab and SBRT in subjects with advanced HCC who have experienced disease progression after sorafenib/lenvatinib therapy, as an estimate of the abscopal effect.
2. To measure the duration and timing of radiographic responses following the combination treatment of pembrolizumab and SBRT in subjects with advanced HCC who have experienced disease progression after sorafenib/lenvatinib therapy.
3. To determine the progression-free survival (PFS), in subjects receiving combination treatment with pembrolizumab and SBRT for advanced HCC who have experienced disease progression after sorafenib/lenvatinib therapy.
4. To determine the overall survival (OS) in subjects receiving combination treatment with pembrolizumab and SBRT for advanced HCC who have experienced disease progression after sorafenib/lenvatinib therapy.
5. To evaluate the safety and tolerability profile of combination treatment with pembrolizumab and SBRT in subjects with advanced HCC who have experienced disease progression after sorafenib/lenvatinib therapy.

1.3 Exploratory Objectives

1. To investigate genomic signatures that may predict responses to pembrolizumab and radiation. This will include Whole Exome Sequencing (WES) and RNA sequencing (RNAseq) on tumor tissue from subjects with advanced HCC who have experienced disease progression after sorafenib therapy. If deemed safe, a second optional biopsy will be performed in consenting patients to compare immune signatures and biomarkers pre and post treatment.

2. To determine levels of circulating tumor DNA (ctDNA) and evaluate methylation profiles from plasma in subjects with advanced HCC who have experienced disease progression after sorafenib/lenvatinib therapy. To examine the associations between these profiles with response to pembrolizumab and SBRT, and between subgroups of patients with all vs not all tumor deposits irradiated.

3. To explore PD-L1 expression as a biomarker predictive of response to combined pembrolizumab and SBRT in subjects with advanced HCC who have experienced disease progression after treatment with sorafenib/lenvatinib, and evaluate the ‘immunoscore’ in HCC.

4. To determine if peripheral analyses of cytokines using electrochemiluminescence may predict the abscopal effect.

5. To explore imaging features correlated with response.

2. BACKGROUND

2.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide, but represents the second leading cause of cancer related mortality, associated with a 5-year survival of less than 10%. It most frequently arises in the setting of chronic liver disease, which may be related to viral hepatitis (Hepatitis B or C infection), alcoholic liver disease, or non-alcoholic fatty liver disease. Many subjects are not eligible for potentially curative treatment in the form of surgical resection or liver transplant, due to either extent of liver dysfunction or advanced tumor stage. Locoregional therapies such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) can prolong survival, but cannot be used in subjects with significant vascular invasion or metastatic disease. HCC is generally considered resistant to most traditional chemotherapy regimens, and the median survival of subjects is approximately 6-9 months without treatment, or shorter if major portal vascular invasion is present.

In subjects with advanced HCC unsuitable for local therapies, and with satisfactory liver function, the current standard of care in Western populations is the oral tyrosine kinase inhibitor (TKI) sorafenib or lenvatinib. The SHARP trial was a phase III study evaluating sorafenib, which randomized 602 subjects to either sorafenib or placebo. In subjects treated with sorafenib, median overall survival was 10.7 months, compared with 7.9 months in those who received placebo (hazard ratio 0.69, 95% CI 0.55-0.87, $p<0.001$).[1] A similar study was carried out in an Asian population, and reported a similar hazard ratio (HR) for OS of 0.68 ($p=0.014$), but with shorter median OS times for subjects treated both with sorafenib (6.5 months) and placebo (4.2 months).[2] This difference in OS may relate to the underlying etiologic factors in HCC development in these populations, with the SHARP study enrolling a majority of subjects with hepatitis C virus (HCV) infection or alcoholic cirrhosis, whereas the Asia-Pacific study was comprised of a majority of subjects with hepatitis B virus (HBV) infection. The recently-reported phase III study of sorafenib alone or in combination with doxorubicin was stopped early due to futility, with a trend toward decreased survival in subjects treated with the combination (HR 1.06, 95% CI 0.8-1.4).[3] More recently the REFLECT study demonstrated that lenvatinib, another multikinase inhibitor, was non inferior to sorafenib. The REFLECT study enrolled patients with BCLC B or C staging, and Childs Pugh Class A. Of note those with more than 50% liver invasion or invasion of bile ducts or portal vein were excluded. Median overall survival was was 13.6 months on lenvatinib vs 12.3 months on sorafenib, with an HR of 0.92 (95% CI = 0.79–1.06), showing non-inferiority of lenvatinib compared to sorafenib.[1]

In subjects who have experienced disease progression on sorafenib or lenvatinib a number of new therapeutic options have been approved recently. For decades many randomized trials of numerous agents had failed to show improved survival compared with placebo, including brivanib, ramucirumab and everolimus.[4-6] The RESORCE randomized phase III study of regorafenib in 573 subjects with progressive HCC after previous sorafenib therapy has reported positive results. The median OS in the regorafenib group was 10.6 months, compared with 7.8 months in the placebo group (HR 0.63, 95% CI 0.50-0.79, $p<0.001$).[7] Furthermore cabozantanib and ramucirumab (when alpha-feto protein > 400

ng/ml) are now approved tyrosine kinase inhibitors but are yet to be reimbursed in Canada. Each provide an improvement in survival over placebo of only 2.2 month and 1.2 months respectively.

2.2 Investigational Agents

2.2.1 Pembrolizumab (a.k.a. MK-3475)

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

2.2.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[8] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[9-12] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[13] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[14] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T-regulatory cells and Natural Killer cells. Expression has also been shown during thymic development on CD4- CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of subjects with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Pembrolizumab was also recently approved for the treatment of subjects with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by a Food and Drug Administration (FDA)-approved test, with disease progression on or after platinum-containing chemotherapy.

2.2.1.2 Preclinical and Clinical Trial Data

Therapeutic studies in mouse models have shown that the administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 and anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promotes CD8+ T-cell infiltration into the tumor and the presence of interferon-γ, granzyme B and perforin, indicating that the mechanism of action involves local infiltration and activation of effector T-cell function in vivo.[15,16] Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB). Clinical trials have demonstrated efficacy using pembrolizumab in subjects with advanced melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma. In addition, recent data demonstrate emerging evidence of single-agent activity in additional tumor types such as mesothelioma, urothelial cancer, ovarian cancer, neuroendocrine carcinoma, and small cell lung cancer.

Immune checkpoint blockade is an attractive therapeutic option in HCC. The majority of HCCs arise in the setting of chronic inflammation, usually secondary to chronic infection with Hepatitis B (HBV) and C (HCV) viruses. This creates an immunosuppressive state in an organ that naturally promotes immune tolerance. Hepatocytes together with other non-parenchymal cells have been shown to express programmed death receptor ligand-1 (PD-L1), contributing to the suppression of effector T cells.[17,18,19] Expression levels of PD-1 mRNA have been shown to correlate with disease course in HBV subjects and post-operative recurrence in HBV-associated HCC,[20,21] and in HCV-associated HCC, infiltrating and circulating CD8+PD1+ T cells correlated with progression and recurrence postoperatively.[22] In a mouse model of HCC, blockade of PD-1 with immunostimulatory monoclonal antibodies extends survival.[23] The interim analysis of a Phase I/II trial of nivolumab in previously treated subjects with HCC demonstrated objective responses in 16% of subjects (n=214) and an estimated survival rate of 71% at 9 months. Results also show the safety profile of nivolumab to be generally consistent with that previously reported in other tumor types.[24]

2.2.1.3 Rationale for Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma and NSCLC subjects is 2 mg/kg Q3W. Information on the rationale for selecting the 200 mg Q3W dose is summarized below.

Keynote-001, an open-label Phase I study, was conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics, and anti-tumor activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated, no dose-limiting toxicities were observed, and no maximum tolerated dose (MTD) identified. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. Additional cohorts at different dose levels and frequencies reported similar

results, with all clinical efficacy and safety data demonstrating a lack of important differences across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide a similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

In a population PK model, developed with data from 476 subjects, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the non-small cell lung cancer (NSCLC) and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor indications.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual subject exposures in the exposure ranges established in melanoma and NSCLC as associated with maximal clinical efficacy and 3) will maintain individual subject exposures in the established safe exposure ranges.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate pembrolizumab dose.

2.2.2 Liver SBRT

Stereotactic Body Radiotherapy (SBRT) has increasingly been shown to have an important role in the treatment of HCC.

Historically conventional external beam radiation to the liver was associated with radiation induced liver toxicity (RILD). Classic RILD refers to a syndrome characterized by anicteric hepatomegaly, elevation of liver enzymes (ALP>AST) and ascites and can progress to liver failure, despite maximal care. Classic RILD is uncommon in modern radiation therapy series, when the dose to the liver can be kept below recommended levels. Technological advances in radiation treatment planning, breathing motion management and image guided radiation therapy (IGRT), have made it possible for ablative doses of

radiation to be delivered safely to focal unresectable HCC, using conformal RT, SBRT or protons. However, a decline in liver function (e.g. as assessed using Child Pugh score or ALBI) 3 months following radiation therapy is seen in 10 – 30 % of patients. Presence and progression of main portal branch HCC may contribute to this, and subsequent improvement in liver function often follows if the vascular HCC responds to radiation therapy (which may be delayed at 3 – 6 months post radiation).

SBRT involves the delivery of high doses of RT in smaller fractions using highly precise techniques therefore minimizing injury to surrounding hepatic parenchyma. Furthermore, cell death may be enhanced by causing vascular injury together with double-strand DNA breakage.
SBRT for the treatment of unresectable HCC was first reported in 1995 and recent studies predominantly in patients with tumors < 6 cm have demonstrated high local control rates of 70 - 90% at 1-2 years.[25-30] In one study of 38 HCC patients previously treated with TACE, 33 – 57 Gy was delivered in 3 fractions, with a 61% 2 year survival.[29] Doses > 42 Gy in 3 fractions were associated with improved local control. In another study of 48 patients with HCC treated
with 3-fraction SBRT (30 – 39 Gy), 11% of patients had a decline in Child-Pugh class, which was more likely if less volume of liver was spared (<800 cc of liver receiving 18 Gy or more).[31] Early studies in Japan have reported survival at 1 year of 99% and 100% in patients with small tumors treated with SBRT, suggesting a potential curative role in this select population.[32,33]

In patients with more advanced HCC, SBRT has also been used successfully. However, individualization of the SBRT dose is required to reduce the risk of toxicity. Interestingly, even non-ablative SBRT doses have been associated with long term control of the irradiated locally advanced HCC, and recanalization of the vascular HCC has been observed.[34] Xi et al reported a 50% one year survival in 41 patients with vascular HCC following 30 – 48 Gy in 6 fractions.[35]

An iso-toxic RT schedule that allows patients with HCC unsuitable for standard therapies to be treated in 6 fractions over two weeks using SBRT was developed at Princess Margaret Hospital (PMH), University of Toronto.[36] The dose per fraction was determined based on the effective volume of normal liver irradiated (Veff), accounting for differences in dose per fraction. When the effective liver volume irradiated was low (Veff < 25%), doses of 54 Gy (9 Gy x 6) were delivered safely to HCCs, with excellent local control. For patients requiring higher volumes of liver to be irradiated (Veff 25-80%), doses from 24 to 54 Gy (4 to 9 Gy x 6) were delivered safely, although local control was reduced. An analysis of the completed phase I and II Toronto SBRT studies of 102 Child-Pugh A HCC patients ineligible for local-regional therapies (38% Hepatitis B, 38% Hepatitis C, 25% alcohol; 55% portal vein thrombosis; 12% extrahepatic disease) treated with SBRT (median dose 36 Gy in 6 fractions) from 2004 to July 2010 found a median survival of 17.0 months and 1 year local control rate of 87%. A dose response for local control was observed, with more sustained local control when 30 Gy in 6 fractions or more was delivered.[34] No classic RILD was seen. However, a decline in Child Pugh score was seen in approximately 30% of patients 3 months following SBRT. Factors significantly associated with toxicity were baseline Child Pugh score (A6 versus A5), lower baseline platelet count, mean liver (minus HCC volume) dose, and dose to 800cc of liver (minus HCC volume, D800cc). There was no toxicity if the mean liver dose (MLD) was < 18 Gy in 6 fractions and the D800cc was < 15 Gy in 6 fractions.[37] In 2012, at Princess Margaret Cancer Centre, a change from 6 fraction SBRT was made to 5 fraction SBRT, and 5 fraction SBRT is now our clinical standard of care and is the SBRT fractionation being tested in a phase III randomized trial (RTOG1112 - https://clinicaltrials.gov/ct2/show/NCT01730937).

In summary, although local control (including sustained stable disease) is likely with modest dose SBRT, even to large HCCs or those associated with vascular invasion, progression outside the irradiated volume is common following SBRT alone (PFS ~ 3-4 months), and there is rationale to combine SBRT with systemic therapies.

2.2.3 Combination of SBRT and pembrolizumab

There is significant biologic rationale for synergy between radiotherapy and immunotherapy, as SBRT may provide an immunologic "adjuvant" for use with checkpoint blockade.[38,39] Early phase II data of combination ICI and radiation in melanoma are promising.[40] Preclinical data suggests that higher doses per fraction, as used with SBRT, are more likely to induce an immune response and abscopal effect.[41-43] The abscopal effect has been seen in several tumor types, including renal cell carcinoma, melanoma and anecdotally in several patients with HCC.[44-47] The combination strategy of ICI and SBRT in HCC has the advantage of inducing locoregional response in liver and vascular disease as well as targeting extrahepatic metastases. A recent orthotopic murine model of HCC has demonstrated the superiority of combination SBRT and anti-PD-1 blockade compared to either modality alone.[48] Other pre-clinical models of combinations SBRT and immune checkpoint blockade have revealed similar results with the abscopal effect only elucidated when immunotherapy was added.[43,49] A mouse model in GBM also evaluated sequence of treatment and a number of clinical studies have demonstrated both in field and abscopal responses to combination therapy.[50-54] Although the most optimal sequencing of treatment is not clear, concurrent treatment appears superior in murine models.[48,55,56]

There is no clinical experience with the combination of anti-PD-1 blockade and SBRT for liver cancer and limited experience with combined check point inhibitors and radiation therapy for any type of cancer. A retrospective study of 127 patients with melanoma treated with ipilimumab and local therapy reported better local control, survival and increased abscopal effects in patients treated with local therapy in addition to ipilimumab, with no increase in toxicity in patients treated with local therapies.[57] The majority of patients received radiation therapy to the brain, the skin or lymph nodes, with 2 receiving radiation therapy to the liver.

A phase III study of 799 patients treated with palliative radiation therapy (8 Gy in 1 fraction) for bone metastases from prostate cancer (CA184-043) reported grade 3/4 toxicity in 26% versus 3% in patients treated with radiation followed by ipilumumab or placebo respectively , consistent with reported toxicity from ipilumumab alone.[58] In a phase I study of 35 patients treated with Ipilimumab and SBRT (50 Gy in 4 fractions), 2 patients treated with concurrent SBRT and ipilumumab developed dose limiting toxicity (grade 3 pancreatitis and lipase elevation); one patient with sequential ipilumumab and SBRT developed grade 3 increase in bilirubin and AST, and 12 of 35 patients (34%) had grade 3 toxicity (colitis in 4), slightly higher than reported grade 3 toxicity post ipilumumab alone (10 – 28%) with no grade 4 or 5 toxicity observed.[59] Clinical benefit was associated with increased peripheral CD8+ T cells, CD8+/CD4+ T cell ratio and proportion of CD8+ T cells expressing 4-1BB and PD-1. There was greater T cell activation in patients receiving liver SBRT versus lung SBRT. Another small study of ipilimumab with SBRT in metastatic melanoma reported responses in 6 of 22 evaluable patients, and manageable toxicity with only 3 patients discontinuing treatment due to adverse events, and grade 3/4 toxicity in 14% of patients.[60]

In summary, there has not been a clear indication that toxicity is increased with the combination of

radiation and ICI, but there is a need for prospective data, especially in HCC.

2.3 Rationale

As discussed above, there is significant interest in using immune checkpoint inhibitors in the treatment of hepatocellular carcinoma. In addition, the use of SBRT has shown promise in treating subjects with hepatocellular carcinoma.

The combination of SBRT and immune checkpoint inhibition with pembrolizumab aims to capitalize on the local control effect of the radiotherapy by combining with a systemically-active agent to increase local response within the radiation field and control disease not encompassed by SBRT.

Objective response rate has been chosen as the primary outcome measure for this study. Although overall survival (OS) is the gold standard for measuring efficacy of cancer treatment, measurement of radiographic response rate is considered an acceptable endpoint for phase II clinical trials, as an effective treatment is considered likely to result in a reduction in tumor size.[61] The use of RECIST 1.1 in HCC has been problematic in subjects treated with anti-angiogenic therapy such as sorafenib, or treatments involving vessel embolization (transarterial chemo-embolization, transarterial radio-embolization, or bland embolization) but both PD-1 checkpoint inhibitors and SBRT have separately been associated with RECIST responses.[24,34] iRECIST adapts RECIST to account for unique response kinetics seen following immunotherapy, by allowing for treatment beyond unconfirmed progression (iUPD) in clinically stable patients, where there after a response may be seen. New lesions are not counted as the sum of measurement (SOM), but are recorded separately and may be considered iUPD until confirmatory progression (iCPD) This is explained in further detail in Section 11.1.4.

The selection of overall response rate includes the lesions treated with SBRT as well as systemic disease not included in the radiation volume. This composite response aims to evaluate the effect of the "treatment package" of pembrolizumab and SBRT, a paradigm in which the SBRT provides high rates of local control in the liver and the pembrolizumab controls systemic disease, and there is potential synergy and/or abscopal effect of using the two in combination. Assessment of response will be performed by a radiologist independent to the conduct of the study. Secondary endpoints will aim to measure the response in tumor lesions outside the SBRT field, an assessment of the abscopal effect described following radiotherapy. Additional secondary efficacy endpoints will include PFS and OS.

2.4 Correlative Studies Background

2.4.1 Correlation between tumor genomic characteristics and response to therapy

Introduction: Immune checkpoint inhibitors (ICIs) are an important novel class of anti-neoplastic agent that may act synergistically with radiation. Biomarkers predicting response to immune checkpoint inhibition and to the potential abscopal effect when combined with radiation are lacking. Thus, to benefit future subjects, we will seek to define novel predictive biomarkers of response. This will require a mandatory biopsy, consisting of 4 x core biopsies and blood samples to support genomic and immune correlative analyses.

These will include but are not limited to:

Germline (blood) and tumor genomic analyses

This research will evaluate whether genetic variation within a clinical trial population correlates with response to the combination treatment under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the subject population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

Next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability etc.), mutational loads and specific genomic signatures that may influence response to ICIs, and also to SBRT. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Tumor DNA and RNA will be extracted from biopsies at diagnosis and banked for planned whole exome sequencing (WES) and whole transcriptome gene expression analysis by RNA sequencing. In patients consenting for a repeat biopsy at 3-6 weeks, tumor specimens will also be banked. This will be offered only when deemed safe by the PI. Specific signatures detected may inform responsiveness or resistance to ICIs, and using data from RNAseq it will be possible to evaluate gene signatures previously shown to be potentially predictive of response to pembrolizumab.[62,63]

Blood analyses

The analysis of circulating tumor DNA (ctDNA) appears to be feasible in early studies in HCC, and correlations of ctDNA may provide important insight into the timelines of response or non-response to immunotherapy and combination treatment.[64] Circulating tumor DNA (ctDNA) will be measured at diagnosis, during SBRT, at 12 weeks and at time of disease progression (20ml per time point). The absolute concentration of ctDNA within peripheral blood plasma will be calculated from the aggregated tumor-specific reads and normalized to the total concentration of cell-free (cf) DNA. At these time points DNA methylation profiles in cfDNA will also be evaluated. Samples of cfDNA will be stored at -80C, to allow for potential future post-hoc quantitative analyses.

PD-L1 Expression and Immunoscore

Tumor samples from this study will be analyzed for percentage PD-L1 expression. PD-L1 protein level, as assessed by IHC in tumor sections, has been shown to correlate with response to pembrolizumab in subjects with NSCLC, and a PD-L1 IHC diagnostic is marketed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (i.e., triple-negative breast cancer, head and neck, and gastric). The burden of tumor infiltrating lymphocytes (TILs) may also predict response to ICIs and provide an 'immunoscore' which can prognosticate in HCC; densities of CD8, CD3, CD45R0 and PD-1 may also be assessed.[65,66]

Cytokine analysis

Predictors of the abscopal effect are of great interest but lacking. Documented rises in antibodies to melanoma specific tumor antigens have been reported and in HCC this the abscopal effect has correlated with a rise in TNF-alpha.[44,50,53] Banked samples may be analyzed using electrochemiluminescence assays for dynamic changes in cytokines of interest as a biomarker predictive of the abscopal effect. These markers will be compared to gene expression profiles and mutational signatures ascertained from tissue analysis.

Imaging
Diagnostic and radiation therapy imaging will also be investigated to explore whether imaging features are associated with molecular biomarkers or clinical outcomes.

2.4.2 Optional future biomedical research

As much remains unknown about genetic signatures and biomarkers in relation to disease response, any remaining samples from consenting patients will be banked for future biomedical research in order to give investigators the ability to further probe any notable results found during protocol-defined correlatives research.

3. SUBJECT SELECTION

3.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

3.1.1 Be willing and able to provide written informed consent/assent for the trial.

3.1.2 Be ≥ 18 years of age on day of signing informed consent.

3.1.3 Have a histologically or cytologically confirmed diagnosis of hepatocellular carcinoma, and at least one measurable lesion as defined by RECIST 1.1/iRECIST. Otherwise eligible subjects, with a radiographic diagnosis of HCC, may be enrolled for screening, but histological confirmation is mandatory prior to initiation of study therapy.

3.1.4 Have current liver function meeting Child Pugh Class A (5-6 points), with no encephalopathy or ascites. Child Pugh status must be calculated based on clinical and laboratory results during the screening period.

3.1.5 Have intrahepatic HCC amenable to SBRT:
- maximum 10 lesions to be treated, and
- total tumor diameter to be treated <20 cm
- No single liver tumor >15 cm in diameter
- No evidence of common or main branch bile duct invasion
- No evidence of direct tumor extension into stomach, duodenum, small bowel, large bowel or diaphragm
- Smaller satellites of HCC or non-definite HCC need not be encompassed within SBRT volumes if needed to respect normal tissue limits.

3.1.6 Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. The subject must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy. In addition, the subject must be willing to give blood for correlative studies, and have no contraindications to this.

3.1.7 Have a performance status of 0 or 1 on the ECOG Performance Scale.

3.1.8 Have demonstrated disease progression, after previous treatment with sorafenib or lenvatinib for advanced or metastatic disease, lasting a minimum of 8 week period, allowing for appropriate interruptions and dose reductions (i.e. second-line systemic therapy for advanced disease after failing 1st line tyrosine kinase inhibitor (TKI)) . Individuals who have discontinued sorafenib/lenvatinib for documented grade 3 or 4 toxicity may be eligible for participation, provided disease progression has been observed since discontinuation of sorafenib/lenvatinib. Occasional subject may have been switched from sorafenib to lenvatinib early before progression due to intolerance and then at progression can be considered eligible having had 1 line of TKI to progression.

3.1.9 Have recovered (to ≤ grade 1) from prior toxicities related to previous treatments at the time of study enrollment, with the exception of alopecia or skin depigmentation.

3.1.10 Be tested for Hepatitis B-Virus surface antigen (HbsAg) status. HBV DNA is not mandated for subjects tested negative for Hepatitis B Virus. Subjects may be included in the study if they have adequately controlled hepatitis B, defined by:

- receiving a nucleoside analog anti-viral drug for 4 or more weeks, and
- serum hepatitis B virus (HBV) DNA level of less than 100 IU/ml via polymerase chain reaction quantification assays prior to enrollment.
- in the case of subjects with known suppressed HBV viral DNA (<100 IU/ml) within 3 months prior to study entry, 7 days nucleoside analog anti-viral drug prior to study inclusion is acceptable.

3.1.11 Be tested for Hepatitis C-Virus antibody (Anti-HCV) status. Subjects with HCV infection (as characterized by the presence of detectable HCV ribonucleic acid (RNA) or anti-HCV antibody) are allowed on study. In addition, subjects with successful HCV treatment (defined as sustained virologic response [SVR] 12 or SVR 24) are allowed as long as 4 weeks have passed between completion of HCV therapy and start of study treatment. HCV RNA is not mandated for subjects tested negative for Anti-HCV during screening.

3.1.12 Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,200 /mcL
Platelets	≥50,000 / mcL
Hemoglobin	≥8 g/dL without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥50 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 34 **umol/l**
AST (SGOT) and ALT (SGPT)	≤ 5 X ULN

Albumin	≥25 g/L
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

3.1.13 Women of child-producing potential must agree to use effective contraceptive methods prior to study entry, during study participation, and for at least 30 days after the last administration of study medication. A serum pregnancy test within 72 hours prior to the initiation of therapy will be required for women of childbearing potential. Men treated or enrolled on this trial must agree to use adequate contraception prior to and for 4 months after completion of pembrolizumab administration.

Highly effective contraception methods include:

• Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

• Male or Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

• Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

• Combination of any two of the following (a+b or a+c, or b+c):

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
Note: Female subjects of childbearing age are defined as follows:
• Subjects with regular menses
• Subjects, after menarche with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
• Women who have had tubal ligation

Female subjects may be considered to NOT be of childbearing potential for the following reasons:

• The subject has undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy or bilateral oophorectomy
• The subject is medically confirmed to be menopausal (no menstrual period) for 24 consecutive months
• Pre-pubertal females. The parent or guardian of young female subjects who have not yet started menstruation should verify that menstruation has not begun. If a young female subject reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward.

3.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

3.2.1. Has received any second-line systemic therapy for advanced HCC after disease progression following sorafenib/lenvatinib therapy, or has had prior radiotherapy to the proposed treatment field (at the discretion of the Principal Investigators).

3.2.2. Is currently participating and receiving experimental treatment as part of a clinical trial, or has participated in a study of an immune checkpoint inhibitor and received study therapy, or used an investigational device within 4 weeks of the first dose of treatment.

3.2.3. Has had a previous solid organ transplant, a diagnosis of immunodeficiency, or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3.2.4. Has liver tumor not amenable to SBRT, as per 3.1.5 above, or has had prior upper abdominal radiation therapy within planned volumes (exceeding standard tolerances).

3.2.5. Has a histological or cytological diagnosis of fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma-HCC.

3.2.6. Has had prior radioembolization or other selective internal radiotherapy treatment to the liver.

3.2.7. Has dual active HBV infection (HBsAg (+) and/or detectable HBV DNA) and HCV infection (anti-HCV Ab(+) and detectable HCV RNA) at study entry.

3.2.8. Has had esophageal or gastric variceal bleeding within 3 months prior to study enrollment.

3.2.9. Has had encephalopathy in the past 6 months, or has clinically apparent ascites at the time of study enrollment.

3.2.10. Has a known history of active TB (Bacillus Tuberculosis).

3.2.11. Hypersensitivity to pembrolizumab or any of its excipients.

3.2.12. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 1 week prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

- Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.13. Has a known history of prior invasive malignancy except if the subject has undergone curative-intent therapy with no evidence of disease recurrence for 2 years prior to study entry. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, low-risk prostate cancer or in situ cervical cancer.

3.2.14. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

3.2.15. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy at a dose of ≤ 10 mg/day of prednisone or equivalent) is not considered a form of systemic treatment.

3.2.16. Has known history of, or any evidence of active, non-infectious pneumonitis/interstitial lung disease.

3.2.17. Has an active infection requiring systemic therapy.

3.2.18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.2.19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.2.20. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

3.2.21. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

3.2.22. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.2.23. Has alcohol related or non-alcoholic steatohepatitis (NASH) related cirrhosis.

3.2.24. Has had a history of significant active or unstable heart disease

3.2.25. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. This study is designed to include minorities as appropriate. However, the trial is not designed to measure differences in intervention effects. The population of Southern Ontario is ethnically diverse and the proportion of different ethnic groups in the community is provided in the table below. Universal access to health care will ensure that there is no discrimination on the basis of race or gender (Guide to Canadian Human Rights Act: www.chrc-ccdp.ca/public/guidechra.pdf). Individual hospital registries and databases do not routinely collect racial data, under the direction of the Canadian Human Rights Code.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

The Central Office Coordinator at the Drug Development Program Central Office will enter eligible subjects on study centrally. All sites should call the Central Office Coordinator (listed on cover page) to verify dose level availabilities. The required forms (Registration Checklist) will be provided upon site activation.

Following registration, subjects should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator (cc the Central Office Coordinator). If a subject does not receive protocol therapy following registration, the subject's registration on the study may be cancelled. The Central Office Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

Prior to registering a subject, each institution must have submitted all necessary regulatory documentation to the Drug Development Program Central Office. The registration checklist will only be sent once this has been received.

No subject can receive protocol treatment until registration with the Central Office has taken place. All eligibility criteria must be met at the time of registration. There will be no exceptions. Any questions should be addressed with the Central Office prior to registration.

To register a subject, the following documents are to be completed by the research nurse or data

manager and sent / faxed to the Central Office Coordinator:
- Signed subject consent form
- Registration Checklist CRF signed by the investigator

To complete the registration process, central office will review the checklist and once eligibility has been confirmed:
- Assign a subject study number
- Assign the subject a dose
- Register the subject on the study
- Fax or e-mail the confirmation worksheet with the subject study number and dose to the participating site

To ensure immediate attention is given to the faxed checklist, each site is advised to also call the Central Office Coordinator listed on the front sheet. Subject registration will be accepted between the hours of 9am to 5pm Monday to Friday, excluding Canadian statutory holidays when the central office will be closed.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dose delays and management of adverse events are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Regimen Description			
Agent	**Dose**	**Route**	**Schedule**
Pembrolizumab	200 mg	IV over 30 minutes	Every 3 weeks
SBRT administered to dominant hepatic HCC			Starting day 2 of cycle 1 pembrolizumab, given in 5 fractions over 5-15 days

5.1.1 Pembrolizumab Dose Selection

The rationale for selection of the dose to be used in this trial is provided in Section 2.2.1.3 Rationale for Dose Selection.

5.1.1.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the STUDY CALENDAR (Section 10). Trial treatment may be administered up to 1 day before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

In general, toxicities from previous cycles of treatment should have returned to Grade 0-1 before the next dose of study medication (see Section 6.1 for specific guidance). Pre-existing Grade 2 toxicities, which did not result in exclusion from the trial, (for example, liver transaminase abnormalities) should be stable.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.1.2 Stereotactic Body Radiotherapy (SBRT) Dosing and Scheduling

All the definite HCC with vascular invasion should be treated by SBRT when safe, up to a maximum of 10 lesions and total diameter of ≤20 cm. However, extrahepatic HCC, all satellites of HCC and non-definite HCC need not be encompassed within the irradiated volumes, especially if normal tissue dose limits cannot be met.

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 (starting on day 2, as per the schema). The preferred inter-fraction interval is 24 hours, with the exception of when luminal OARs are at their maximal dose, when it is preferred that the first two fractions are to be delivered on day 2 and 3 and other fractions every other day. All lesions may be treated on the same day, or alternative lesions may be treated on alternate days, as long as the overall treatment time is 15 days at maximum.

5.1.2.1 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 dose to multiple PTVs may be different. The goal is to use the highest allowable prescription dose to the primary target, while respecting normal tissue constraints. The minimal planned prescription dose to PTVs is 27.5 Gy.
Given the novelty of this combination, and the potential for overlapping hepatic toxicity, the first 10 patients will have to meet all the following additional liver dosimetric constraints:

1) Mean liver (minus gross HCC tumor volume) dose < 15 Gy in 5 fractions.
2) D800cc ≤ 18 Gy in 5 fractions
3) Biologically corrected normal tissue complication probability (NTCP) < 0.5%

If 2 or fewer patients of the first 10 patients experience grade 3 hepatic toxicity at this dose, we will increase to standard dosing. If 3 or more patients experience grade 3 toxicity, or if any patients experience grade 4/5 toxicity in first 3 months following SBRT, these dose constraints will be maintained for all patients on study and modification of all SBRT dose constraints will be considered.

5.1.2.2 Dose Specifications

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

5.1.2.3 Dose Prescription

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

In the absence of adjacent GI luminal structures that may limit dose, the PTV dose prescription should be as high as possible based on mean liver dose (MLD, defined as the mean dose to the liver minus all GTVs), with 6 potential dose levels. Note, no variations in mean liver dose are permitted.

Table 2: SBRT Dose Prescription

Priority Constraint	**Prescription Dose**	
Allowed MLD (Gy)*	Planned Prescription Dose (Gy)	If the max allowed MLD in exceeded at this planned dose
13.0	50	Reduce to 45 Gy and re-evaluate
15.0	45	Reduce to 40 Gy and re-evaluate
15.0	40	Reduce to 35 Gy and re-evaluate
15.5	35	Reduce to 30 Gy and re-evaluate
16.0	30	Reduce to 27.5 Gy and re-evaluate
17.0	27.5	Ineligible

*< 15.0 Gy for the first 10 patients, regardless of prescription dose

- Vascular tumor thrombosis (e.g., portal vein thrombosis) dose should be treated to the same dose as the parenchymal HCC. However, lower doses are acceptable if required to maintain normal tissue limits, since the cancer density may be lower than parenchymal HCC. Non-tumor bland thrombosis is strongly recommended to NOT be irradiated, to reduce the overall volume irradiated.

- Maximum dose within PTV = 150%. If multiple PTVs exist, 150% of the maximal PTV prescription dose is permitted for all PTVs. Concomitant boost to the GTV to 1-2 dose levels above the prescription dose are recommended, and it is desirable to have a hot spot of at least 40 Gy in the GTV if possible.

- Maximum dose outside PTV = 120% of the maximal PTV prescription.
- Efforts should be made to keep the prescription dose and the 30Gy isodose as conformal as possible.
- Different isodoses may cover different PTVs. If multiple PTVs, the MLD should be evaluated with the prescription dose corresponding to the highest dose level that any PTV is treated. Queries should be directed to the study PI.

5.1.2.4 Technical Factors

Megavoltage equipment with photons of at least 6MV, capable of daily image guidance, with a multileaf collimator for intensity modulation is required. Inverse-planned IMRT, forward planned IMRT and volumetric modulated arc therapy (VMAT) are to be used for planning. CT based planning is required, with a minimum of 5 beam angles. Image guided radiation therapy (IGRT) is mandatory. Breathing motion management is recommended if breathing motion is > 5 mm. Breathing motion assessed on 4DCT and adequately treated with PTV margins < 20mm is permitted.

5.1.2.5 Localization, Simulation and Immobilization

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

Treatment planning CT scans will be required to define GTV. Multi-phasic IV contrast is recommended for the planning CT (arterial phase and/or delayed phase imaging recommended for GTV delineation, and venous phase for portal vein thrombosis delineation).

Exhale breath hold CT or average phase CT (from 4D CT) may be used as the baseline CT for radiation therapy planning. CT scans obtained during free breathing may not be used for planning. CT scans used for target delineation are recommended to be multi-phase IV contrast scans obtained in exhale breath hold. Exhale breath hold is preferred as it most often is closer to the average position than inhale breath hold, and exhale is more reproducible than inhale. If IV contrast scans cannot be obtained at the time of radiation planning, IV contrast CT scans from diagnostic radiology may be fused to the primary planning dataset to aid in target definition. If contraindications to IV CT contrast exist, IC contrast multiphase MR can be used to help define GTV. Diagnostic MR imaging can be imported to the planning system to aid in target delineation.

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

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

All patients will have image guidance at the time of each radiation fraction. Cone beam CT is the preferred image guidance.

5.1.2.6 Treatment Planning/Target Volumes

The **Gross Tumor Volume (GTV) is defined as all suitable parenchymal and vascular HCC** visualized on contrast enhanced CT and/or MRI, most often best seen on arterial phase (as hyperintensity) and/or venous or delayed phase (as hypointensity relative to liver). GTVp1 should represent the 'primary parenchymal (=p) dominant (=1)' GTV, upon which primary QA will be based. Subsequent lesions can be labeled as GTVp2, GTVp3, GTVp4 and GTVp5). If 'p' is not included following "GTV", the lesion will be assumed to be parenchymal. Vascular HCC thrombi (GTVv) most often are best seen on venous phase imaging as hypointensity relative to the contrast in the vessel. Vascular HCC may be combined with parenchymal HCC (labeled as GTVp or GTVpv) if they are to be treated to the same dose.
Non-tumor thrombi should not be considered as GTV; they should be excluded from contouring
The prescription dose should be annotated to each GTV after the final plan is complete (e.g. GTVp1_50 for a 50Gy target).

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

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

Standard target and organ at risk nomenclature will be used.

Heterogeneity Corrections: All dose distributions shall include corrections for tissue heterogeneities. Arterial vascular contrast from the planning dataset is recommended to be converted to water equivalent

density if used for planning. Planning datasets without intravenous contrast may be used for planning.

Planning target volumes around luminal GI tissues are encouraged so that the steepest dose gradients of doses higher than the maximal allowable luminal GI doses are outside the PRV. PRV magnitude will be individualized based on an estimate of expected change day-today (5 mm to 30 mm).

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

Critical Structures Maximal Doses
Dose values in this section should be read as physical dose in 5 fractions. Note these doses have been modestly reduced from our present standard, with the goal of reducing the risk of toxicity.

Esophagus max (to 0.5 cc):	30 Gy
Stomach max (to 0.5 cc):	29 Gy
Duodenum max (to 0.5 cc):	29 Gy
Small bowel max (to 0.5 cc):	29 Gy
Large bowel max (to 0.5 cc):	30 Gy
Cord + 5 mm max (0.5cc):	25 Gy
Kidneys: Bilateral mean dose	< 10 Gy

-OR-
If there is one kidney mean dose > 10Gy, remaining (or only) kidney V10Gy < 10%

The following organ dose constraints are strongly advised to be met, but are not mandatory:

Stomach (to 5 cc):	< 25 Gy
Duodenum (to 5 cc):	< 25 Gy
Small bowel (to 5 cc):	< 25 Gy
Liver minus all GTVs:	>700cc and D800cc ≤ 18 Gy
Heart max (30cc):	< 30 Gy
Skin (external) max (0.5 cc):	< 32 Gy
Chest wall max (0.5 cc):	< 50 Gy
Gallbladder max (0.5 cc):	< 55 Gy
Common bile duct max (0.5 cc)	< 50 Gy*

*Even though the bile duct is not often well visualized, it is always within the portal region and may be within high dose volumes for central targets, so efforts to reduce hot spots in this region are warranted.

Peer review of all SBRT plans is required prior to starting SBRT (either one-on-one or at GI or SBRT quality assurance rounds) by another radiation oncologist.

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

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

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

The following **Table 3** describes variations and deviations in the prescription dose (dose covering 95% of the PTV). **Treating "per protocol" should always be the planning intent.**

Table 3: Variations and Deviations in Prescription Dose

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

*Note that lower doses than the dose-allocation schedule are acceptable if they are required due to adjacent luminal GI structures that may limit the deliverable dose.

Compliance for Critical Structures (organs at risk, OARs)
If non-hepatic OARs limit the prescription dose, the highest dose (from the 6 prescription doses listed in **Table 2** above) should be used, while maintaining OAR dose constraints.

Table 4: Variations and Deviations due to Organs at Risk

Non-liver OARs	Per protocol	Variation acceptable	Deviation unacceptable
Esophagus max (to 0.5 cc):	30 Gy	> 30 but ≤34 Gy	> 34 Gy
Stomach max (to 0.5 cc):	29 Gy	>29 but ≤32 Gy	> 32 Gy
Duodenum max (to 0.5 cc):	29 Gy	>29 but ≤32 Gy	> 32 Gy
Small bowel max (to 0.5 cc):	30 Gy	>30 but ≤32 Gy	> 32 Gy
Large bowel max (to 0.5 cc):	30 Gy	>30 but ≤34 Gy	> 34 Gy
SpinalCord_05 + 5 mm max (0.5cc):	25 Gy	>25 but ≤28 Gy	> 28 Gy
Kidneys: Bilateral mean dose	≤10 Gy	>10 but ≤12 Gy	> 12 Gy

Table 5: Acceptable & Unacceptable Dose Deviations

Prescription Dose	Liver (minus GTV) mean dose	
	Per protocol (acceptable)	Deviation (unacceptable)
50 Gy	≤13 Gy	> 13 Gy
45 Gy	≤15 Gy	> 15 Gy
40 Gy	≤15 Gy	> 15 Gy
35 Gy	≤15.5 Gy	> 15.5 Gy

30 Gy 27.5 Gy	≤16 Gy ≤17 Gy	> 16 Gy > 17 Gy

5.2 General Concomitant Medication and Supportive Care Guidelines

Initiation of Proton Pump Inhibitors (PPIs) prior to starting SBRT should be considered for subjects whose treatment plan will contain significant volumes of stomach or duodenum. In these patients, non-steroidal anti-inflammatory drugs should be avoided where possible.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy not specified in this protocol for the treatment of HCC. See Section 5.3.2 for details on radiotherapy for oligoprogressive disease
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than the following:
    - To modulate symptoms from an event of clinical interest of suspected immunologic etiology
    - Physiologic doses of prednisone 10 mg (or equivalent) per day
    - Inhaled steroids for management of asthma
    - Use of prophylactic corticosteroids to avoid allergic reactions (e.g., IV contrast day)
    - Topical steroids for management of skin reactions

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describe other medications which are prohibited in this trial.

Any other medication which is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator.

5.3 Duration of Therapy

In the absence of treatment delay / discontinuation due to adverse event(s), treatment may continue until one of the following criteria applies:

- Confirmed disease progression by iRECIST, as defined by Section 11.1.4
- Clinical evidence of disease progression, in the opinion of the Investigator, such that

continuing treatment would not be beneficial for the study subject. Note that further SBRT may be considered for oligoprogressive disease as per Section 5.3.2, and re-challenge with pembrolizumab may be considered in circumstances listed in Section 5.3.1.

- Women who become pregnant or are breastfeeding
- Sexually active subjects who refuse to use medically accepted forms of barrier contraception (e.g. male condom, female condom) during the study
- Termination of the protocol by a regulatory agency or Sponsor, or study medication can no longer be provided
- Significant non-compliance with the protocol schedule in the opinion of the investigator
- Subjects requiring a delay in treatment beyond the allowed timeframe.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event as defined in Section 7
- Subject decides to withdraw from the study
- General or specific changes in the subject's condition which render the subject unacceptable for further treatment in the judgment of the investigator.
- Necessity for treatment with another anti-cancer treatment prohibited by this protocol
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.
  Note: 24 months of study medication is calculated from the date of first dose.

5.3.1 Retreatment with Pembrolizumab

Subjects who stop pembrolizumab with SD/iSD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open (accrual may be completed, but patients still in follow-up) and the subject meets the following conditions:

Either

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR/iCR according to RECIST 1.1/iRECIST, and
  - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
  - Received at least two treatments with pembrolizumab beyond the date when the initial CR/iCR was declared

OR

- Had SD/iSD, PR/iPR or CR/iCR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab

- Did not receive any anti-cancer treatment since the last dose of pembrolizumab, except for SBRT to oligoprogressive lesion (see Section 5.3.2)

- Has ECOG performance status of 0 or 1

- Demonstrates adequate organ function as listed in Inclusion Criteria (Section 3.1)

- Female subjects of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.

- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

5.3.2 SBRT to Oligoprogressive lesions

It has been observed that patients with overall stable or responding disease may develop a small number of new or progressive tumor deposits during active treatment. Such patients are likely to benefit from continuing on study treatment, and may be eligible for additional SBRT to these lesions if the following criteria apply:

- Excepting the oligoprogressive lesions, the best overall response is SD/iSD, PR/iPR or CR/iCR by RECIST 1.1/iRECIST
- The oligoprogressive lesions has been noted at the second or later CT assessment of disease
- 5 or fewer progressive or new lesions are noted
- The patient has evidence of ongoing clinical benefit – no deterioration in clinical or laboratory parameters suggestive of overall worsening of disease or clinical condition
- The oligoprogressive lesions are amenable to SBRT – not within previous SBRT field, and SBRT can be delivered with an acceptable safety profile in the opinion of the Investigator. This includes extrahepatic HCC and selected intrahepatic HCC (if the estimates cumulative dose to the liver is within specified dose limits)

Patients with oligoprogressive lesions that fit the above criteria may be eligible for further SBRT, and should be discussed with the Principal Investigator/Sponsor.

5.4 Duration of Follow Up

Subjects removed from therapy for reasons other than progressive disease/iCPD will be followed at intervals of 90 days (±14 days) for disease status until progression or initiation of alternative therapy. Follow-up visits can occur remotely via telephone, Ontario Telemedicine Network (OTN), or other appropriate virtual communication if it is in patient's best interest, at the discretion of the Investigator. Subjects who withdraw for refusal will no longer be followed. All subjects will be followed for survival every 90 days (±14 days) for survival status until death via telephone, in-person visit, or via medical records.

Table 6: Follow-up Guideline

		Follow-Up Period			
		Off Treatment Visit: 4 weeks ± 7 days from the End of Study Drug Administration	Progression Follow-Up: every 3 months ± 14 days after the Off Treatment Visit *	Adverse Event Follow-Up: until resolution or stabilization of adverse event(s)	Survival Follow-Up: every 3 months ± 14 days after the Off Treatment Visit
Reason Subjects Removed from study	Objective Disease Progression	X		X	X
	Clinical Progression/ Symptomatic Deterioration	X	X	X	X
	Adverse Events or clinically significant lab value	X	X	X (weekly FU for 4-weeks, then monthly)	X
	All other subjects	X	X	X	X

* Confirmed disease progression (iCPD) is defined according to iRECIST.
** See section 7.6 for Adverse Event Follow-Up details

5.5 Criteria for Removal from Study

Subjects will be removed from study when any of the following criteria applies:

- Death
- Withdrawal of consent
- Lost to follow-up
- Sponsor-Investigator termination of the study
- Termination of the study by a regulatory body

The reason for study removal and the date the subject was removed must be documented in the Case Report Form.

6. DOSING DELAYS/MODIFICATIONS AND TOXICITY MANAGEMENT

6.1 Pembrolizumab Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 7 below. See Section 5.2 for supportive care guidelines, including use of corticosteroids.

Table 7: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without

	Recurrent Grade 3 or Grade 4	Permanently discontinue	or equivalent) followed by taper	fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[1]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

			equivalent) followed by taper.	
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

NOTE:
1. For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).
2. Non-irAE will be managed as appropriate, following clinical practice recommendations.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled cycle day 1 delay, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Subjects experiencing a toxicity requiring a dose interruption may be eligible for rechallenge if the above criteria are met, at the discretion of the treating investigator. A subject who experiences a recurrence of the same toxicity at the same grade or higher should permanently discontinue pembrolizumab.

6.2 Guidance for Diagnosis and Management of Hepatic Events of Clinical Interest (ECIs)

In addition to overdose, hepatic ECIs will include any of the following events. All of these events will require holding pembrolizumab treatment and notification of the Sponsor within 24 hours. Refer to Section 7 for reporting guidelines.
All cases of retreatment and permanent discontinuation must be reported to the Sponsor and recorded in the database.

a) ALT:
   i) Among subjects with baseline ALT <2×ULN: ALT ≥5×ULN
   ii) Among subjects with baseline ALT ≥2×ULN: ALT >3× the baseline level
   iii) ALT >500 U/L regardless of baseline level
   (Subjects with ALT >5×ULN at baseline are not eligible for enrollment)

b) AST:
   i) Among subjects with baseline AST <2×ULN: AST ≥5×ULN
   ii) Among subjects with baseline AST ≥2×ULN: AST >3× the baseline level
   iii) AST >500 U/L regardless of baseline level
   (Subjects with AST >5×ULN at baseline are not eligible for enrollment)

c) Total Bilirubin:
   i) Among subjects with baseline levels <22 umol/L: a value of >34 umol/L
   ii) Among subjects with baseline levels that are ≥22 umol/L: a value ≥2× the baseline level
   iii) Total bilirubin >51 umol/L regardless of baseline level
   (Subjects with total bilirubin >34 umol/L at baseline are not eligible for enrollment)

d) Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
   i) New onset clinically detectable ascites
   ii) Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
   iii) Encephalopathy
   (Subjects with clinically apparent ascites or encephalopathy, or untreated varices at baseline are not eligible for enrollment)

Immediate assessment
<u>All subjects</u>

- All subjects should be evaluated according to directions below within 72 hours of alert for non-overdose ECI
- Procedures:
  - Obtain an opinion from a hepatologist
  - Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, Epstein-Barr virus serology, and cytomegalovirus serology

- Assess for ingestion of drugs/supplements with hepatotoxic potential
- Assess for alcohol ingestion
- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, bilirubin, ALP, INR, and CBC with differential
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated by hepatologist

Hepatitis C-Infected Subjects (including subjects who previously achieved SVR 12)

- In addition to the above, measure HCV RNA viral load

Hepatitis B-infected Subjects

- HBV DNA, HBsAg, anti-HBs, HbeAg and anti-Hbe
- Subjects should be questioned about compliance with the use of anti-viral agents.

Permanent Discontinuation Criteria for Subjects with Non-overdose Hepatic ECI
Therapy should also be permanently discontinued for any of the following:

- ALT >20×ULN
- CP score of ≥9 points
- Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
- New onset of clinically detectable ascites that cannot be managed with appropriate treatment
- Encephalopathy
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related
- Other subjects may be eligible for treatment interruption (and potential re-start) of pembrolizumab after discussion with the Sponsor.

Diagnosis and Management of Non-Overdose Hepatic ECIs
HCC subjects are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in ~1% of subjects who received pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC subjects.

a. Hepatitis B Flare
Hepatitis B flares are characterized by rapid elevations of ALT and AST to >5×ULN and/or >3× baseline. ALT elevation to ≥10×ULN is common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP). This is accompanied (or preceded) by a detectable rise in HBV viral DNA in serum. An episode of elevated transaminases without increase in HBV DNA is not attributable to a viral flare.

Among subjects with HBV, a flare should be considered if this pattern is observed and there is no evidence of an alternative etiology. Guidelines for subjects with a diagnosis of HBV flare are as follows:

- Care should be instituted in consultation with a hepatologist.
- For subjects who have detectable HBV DNA, re-institute anti-viral therapy.

- If the subject is clinically stable, pembrolizumab dosing may be interrupted for up to 12 weeks. Subjects should undergo weekly laboratory tests including: AST, ALT, ALP, bilirubin, INR, HBsAg, HBV DNA (if detected at the onset of the flare). Obtain anti-HBe, anti-HBs, and HBV DNA levels (if not detected at the onset of the flare) every 2-3 weeks.
- If ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and subjects are clinically stable, subjects may restart pembrolizumab treatment. If these conditions are not met, then pembrolizumab treatment should be permanently discontinued.

b. Hepatitis C Recurrence or Flare

Subjects who achieved sustained viral remission for 12 months (SVR 12) and subjects with ongoing HCV infection are eligible for enrollment. In rare circumstances, HCV subjects who achieve SVR 12 may relapse at later time points. Relapse is characterized by detection of HCV RNA, often accompanied by ALT elevations to >5×ULN. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP).

Among subjects with uncontrolled hepatitis C, virologic flares are possible. Hepatitis C flares are characterized by rapid elevations of ALT and AST to >5×ULN and/or >3× baseline along with a rise in HCV RNA. ALT elevation to ≥10×ULN and a 1 log elevation in HCV RNA level are common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP). Laboratory abnormalities secondary to flare or recurrence are typically observed for 3-5 weeks.

Guidelines for subjects with recurrent HCV infection or an HCV flare are described below:

1) Recurrent HCV infection:

If the subject entered the study with undetectable HCV RNA, and has confirmed detectable HCV RNA (2 specimens, 1 week apart) at time of event, then the subject has experienced a late HCV relapse or a recurrent infection.

- Question the subject about use of injection or inhalation drugs
- At the time of first detection of HCV RNA, send a specimen for HCV genotyping
- Measure AST, ALT, ALP, bilirubin and INR weekly
- Measure HCV RNA levels every 2 weeks
- Therapy with HCV anti-viral treatments should be strongly considered.

2) HCV Flare:
   - At the time of first detection of HCV RNA, send a specimen for HCV genotyping
   - Measure AST, ALT, ALP, bilirubin, INR weekly
   - Measure HCV RNA levels every 2 weeks
   - Therapy with HCV anti-viral treatments should be strongly considered.

3) For both recurrent infection and HCV flare: if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the subjects are clinically stable, subjects may restart pembrolizumab treatment. If these conditions are not met, then pembrolizumab treatment should be permanently discontinued.

c. Immune-related hepatitis

1) Description

Immune-related hepatitis due to pembrolizumab should be suspected if any of the following is seen:

- AST or ALT baseline values are less than 2×ULN, and AST or ALT laboratory values increase to ≥5×ULN
- Among subjects with baseline ALT or AST ≥2×ULN, levels increase to >3× the baseline level
- AST/ALT >500 U/L regardless of baseline level
- Among subjects with baseline levels <22 umol/L: a value of >34 umol/L
- Among subjects with baseline levels that are ≥22 umol/L: a value ≥2× the baseline level
- Total bilirubin >51 umol/L regardless of baseline level

Immune-related hepatitis is a diagnosis made after excluding other possible etiologies for the change. Viral flare (if applicable), biliary or vascular obstruction, infection, medications, and alcohol use must be ruled out (see below).

2) Management

- Interrupt pembrolizumab treatment.
- Start IV corticosteroid (methylprednisolone 1-2 mg/kg/day) followed by oral corticosteroid (1-2 mg/kg/day).
- Monitor with biweekly laboratory tests including AST, ALT, bilirubin, ALP, and INR.
- If symptoms and laboratory tests resolve to Grade ≤1 or baseline (if abnormal at baseline), taper steroids over 28 days. Pembrolizumab treatment may be restarted after steroid treatment has been tapered to prednisone ≤10 mg/day (or equivalent dose of another agent).
- If laboratory abnormalities do not resolve within 3 weeks, or steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks, or subjects show evidence of decompensation to CP C status or have esophageal or variceal bleeding at any point, treatment must be permanently discontinued.
- Consultation with a hepatologist is advised

d. Other Hepatic Events of Clinical Interest

- Infection should be ruled out with cultures of blood, urine, and ascites (if possible), as well as chest x-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be started.
- If bilirubin is elevated above baseline, magnetic resonance cholangiopancreatography or Doppler ultrasound should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.
- A careful review of drugs, including herbal and alternative medications, should be obtained, and alcohol use should be ruled out. See Section 5.2 for drugs which may interfere with hepatic function.
- For all of these cases, subjects may resume pembrolizumab treatment if they are clinically stable after appropriate therapy or discontinue the causative agent, as long as laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks.
- Treatment must be permanently discontinued if the subject is off pembrolizumab therapy for

infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have esophageal bleeding, or become Child-Pugh C at any point.

6.3 Rescue Medications & Treatment of Pembrolizumab-Related Toxicities

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Hepatic**:

Guidance for Diagnosis and Management of hepatic dysfunction can be found in Section 6.2

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

- **Table 8** below shows treatment guidelines for subjects who experience an infusion reaction associated with pembrolizumab.

Table 8: Management of Infusion Reactions

NCI CTCAE Grade	Management	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6.4 Radiation Therapy Toxicity Assessment During Therapy

Expected toxicities from SBRT are listed in Section 7.1.1.2. 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 is <51 mmol/L, Child score is A5-6 and the treating physician recommends continuation. Otherwise, a delay in radiation therapy should occur with possible

continuation of radiation if it resolves. If there is evidence of rapid changes in liver function suggestive of developing toxicity, or if the investigator has concerns regarding the clinical status of the subject, a delay in radiation therapy should be considered even if the criteria below are not met.

If the patient discontinues radiation therapy prematurely, the patient may be considered for further pembrolizumab, if criteria for treatment (see Section 6.1) are met within the allowed time window, and at the discretion of the treating Investigator.

Table 9: Radiation Therapy Toxicity and Suggested Modification

Toxicity	Modification
Hematologic Toxicities	
Grade 1-2	Continue radiation
Grade 3	Hold radiation until ≤ grade 2, then resume
Grade 4	Hold radiation 1 week and until ≤ grade 2, then resume
Gastrointestinal Toxicities	
Grade 1-2	Continue radiation
Grade 3-4 diarrhea	Hold radiation until ≤ grade 2, then resume
Grade 1-2 nausea or vomiting	Initiate anti-emetics prior to radiation and as needed and continue radiation
Grade 3 nausea or vomiting	Hold radiation until ≤ grade 2, then resume with anti-emetics prior to radiation and as needed
Hepatic Dysfunction	
Bilirubin 22-51 umol/L	Continue radiation
Bilirubin > 51 umol/L	Hold radiation until bilirubin improves to ≤ 51 mmol/L; treat as per hepatic ECI (Section 6.2) Consider resuming radiation only if rapid improvement.
Grade 1-2 AST/ALT	Continue radiation
Among subjects with baseline ALT <2×ULN: ALT ≥5×ULN **Among subjects with baseline ALT ≥2×ULN: ALT >3× the baseline level**	Hold radiation until bilirubin improves to ≤ grade 2; treat as per hepatic ECI (Section 6.2). Consider resuming radiation only if rapid improvement
Child-Pugh Score > 7	Hold radiation until improves to Child-Pugh Score ≤ 7
Other non-hematologic toxicities	
Grade 1-2	Continue radiation
Grade 3	Hold radiation until improves to ≤ grade 2, then resume
Grade 4	Discontinue radiation

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 List of Adverse Events and Reporting Requirements

This study will utilize the CTCAE v4.0 for toxicity and Adverse Event reporting. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE v4.0.

7.1.1 Expected Adverse Events and Protocol-Specific Expedited Adverse Event Reporting for Investigational Agent(s)

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting as an SAE in addition to routine reporting.

In addition, hospitalizations for routine procedures, protocol treatment, blood sampling, investigations and tissue biopsies are NOT considered SAE in this protocol.

7.1.1.1 Expected Adverse Events for Pembrolizumab

Refer to the current Pembrolizumab Investigator's Brochure for detailed information on adverse events.

Most Frequently Reported (Incidence ≥ 5%) Adverse Events Presented by decreasing Frequency and Considered Drug-Related by the Investigator in Participants Treated with Pembrolizumab

Likely (10-30%)

- Fatigue
- Pruritis
- Arthralgia
- Nausea
- Diarrhea
- Rash or itch

Less likely (<10%)

- Decreased appetite
- Asthenia
- Vitiligo
- Fever
- Hypothyroidism
- Myalgia
- Infusion reaction
- Hyperthyroidism

Rare (1% or less)

- Pituitary disorders
- Autoimmune hepatitis
- Myositis
- Autoimmune nephritis
- Pericarditis
- Pancreatitis
- Diabetes Mellitus
- Uveitis
- Hypoadrenalism
- Myocarditis
- Myasthenia
- Sarcoidosis
- Encephalitis
- Stepven-Johnson Syndrome and Toxic Epidermal Necrolysis
- Myelitis

Most Frequently Reported (Incidence ≥ 0.2%) Serious Adverse Events Presented by Decreasing Frequency and Considered Drug-Related by the Investigator in Participants Treated with Pembrolizumab

- Pneumonitis
- Colitis
- Diarrhea
- Pyrexia
- Hypopituitarism
- Pneumonia
- Adrenal insufficiency
- Hyponatraemia
- Dyspnoea
- Hyperthyroidism
- Type I Diabetes Mellitus
- Hypopituitarism
- Hypothyroidism
- Vomiting
- Aspartate aminotransferase increased
- Pericardial effusion
- Pleural effusion
- Alanine Aminotransferase increased
- Interstitial lung disease
- Autoimmune Hepatitis

7.1.1.2 Expected Adverse Events for SBRT

Very likely (80-90%)

- Fatigue (which generally resolves after radiation therapy is completed)
- Skin irritation, redness, itchiness, discomfort
- Temporary changes in blood work, without symptoms

Less likely (30%)

- Nausea, vomiting (during therapy) – more common if stomach or GI tract irradiated
- Diarrhea or sensitivity to food – more common if GI tract irradiated
- Gastritis, esophagitis, duodenitis, colitis – more common if relevant portion of the GI tract is irradiated
- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (<10% permanent changes)
- Chest wall pain, rib fracture (< 10%)

Less likely, but serious (<1-25%)

- Radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of ALP 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 (~25%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v4.0. A copy of the CTCAE v4.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

Associated with the use of the treatment*:* There is a reasonable possibility that the experience may have been caused by the drug/biologic.

Life threatening adverse treatment experience: Any adverse drug/biologic experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

Serious adverse treatment experience: Any event is an AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE (The subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death).
- Hospitalization or prolongation of existing hospitalization (Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE).
- A persistent or significant disability/incapacity (A substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption).
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization or the development of drug dependency or drug abuse).

Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported as an SAE. A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy).

Events not considered to be serious adverse events are:

- hospitalizations for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition,
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen,
- admission to a hospital or other institution for general care, not associated with any deterioration in condition, or
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Any SAE occurring after the subject has provided informed consent and until 4 weeks after the subject has stopped study participation must be reported. This includes the phase in which the study protocol interferes with the standard medical treatment given to a subject (e.g. treatment withdrawal during screening phase, change in treatment to a fixed dose of concomitant medication). Serious adverse events occurring more than 4 after study discontinuation need only be reported if a relationship to pembrolizumab or SBRT is suspected.

Unexpected adverse treatment experience: Any adverse drug/biologic experience, the nature, frequency, or severity of which is not consistent with the product monograph, or not consistent with the risk information described above as a protocol-specific expected adverse event (see "Expected Adverse Events and Protocol-Specific Expedited Adverse Event Reporting Exclusions", above).

Pembrolizumab Overdose: For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is attributed to the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

7.3 Serious Adverse Event Reporting

7.3.1 Sponsor Notification

Any serious adverse event or event of clinical interest must be reported to the Central Office within 24 hours of the Investigator at the site learning of the event by a completed SAE form. The adverse event must be completely described in the case report form.

The Central Office will provide expedited reports of on-study SAEs to Health Canada and Merck for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Investigator Brochure), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

All adverse signs and symptoms which occur during or following the course of drug administration must be reported in detail on the subject's case report form. This description is to include the nature of the sign or symptom, time of onset in relation to drug application, duration, severity, and possible relationship to drug, required therapy, and outcome. The subject should be followed until the adverse reaction is resolved, or until in the opinion of the Principal Investigator, reversal of the reaction is not likely to occur.

7.3.2 SAE Follow-up

Follow-up SAE reports is subject to the same timelines as the initial report, and is sent to the same parties to whom the original Serious Adverse Event Form was sent. A new serious adverse event form is completed for the follow-up, stating that this is a follow-up to the previously reported serious adverse event and giving the date of the original report. Each re-occurrence, complication or progression of the

original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or discontinued study participation.

The Sponsor-Investigator and Institution will assist Merck in investigating any SAE and will provide any follow-up information reasonably requested by Merck.

7.3.3 REB Notification of SAEs

Investigators must notify their Research Ethics Boards (according to their local REB policies) and file the report in their study files. Documentation as outlined below must be maintained for reportable SAEs. Documentation that serious adverse events (SAEs) have been reported to REB must be forwarded to the Central Office and kept on file at the Centre. Documentation can be any of the following:

- letter or email from the REB acknowledging receipt
- stamp from the REB, signed and dated by REB chair, acknowledging receipt
- letter or email demonstrating the SAE was sent to the REB

7.3.4 Health Canada SAE Reporting

All serious, unexpected adverse drug reactions must also be reported by the Central Office to Health Canada within 15 days if the reaction is neither fatal nor life threatening, and within 7 days if the reaction is fatal or life threatening.

As Princess Margaret Cancer Centre is the sponsor delegate of this study in Canada, the Central Office of this study will be responsible for reporting all serious unexpected adverse events to Health Canada.

7.3.5 SAE Reporting to Merck

To ensure subject safety, each serious adverse event or hepatic event of clinical interest must also be reported by the Central Office to Merck Global Safety (in English) within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related (Attn: Worldwide Product Safety; FAX 215 993-1220). Follow-up information about a previously reported serious adverse event must also be reported within 24 hours of the Investigator-sponsor receiving it. The SAE Report Form must indicate the relationship to study treatment and be signed by the investigator. All reports of overdose with and without an adverse event must be reported within 24 hours to the Central Office, and within 2 working days by the Central Office to Merck Global Safety.

7.4 Routine Adverse Event Reporting

For abnormal laboratory values, it is the responsibility of the Principal Investigator to assess the clinical significance of each abnormality. Only abnormal laboratory values that can be assessed for grade using CTCAE v4.0 will be documented. The Investigator will determine whether abnormal laboratory values are considered clinically significant and represent AEs based on their medical judgment.

Data on all adverse experiences/toxicities regardless of seriousness must be collected for documentation purposes only.

Clinical Laboratory Abnormalities:

All abnormal laboratory values should be captured on source documentation and assessed for clinical significance by the Investigator at the site. Only abnormal laboratory values deemed clinically significant should be listed as AEs in the CRFs. All clinically significant abnormal laboratory results will be followed up until the related AE resolves, returns to < grade 1 or baseline value in the follow-up period. Clinically significant laboratory abnormalities will be dictated in the clinic notes. Additionally, laboratory abnormalities resulting in an intervention are considered to be clinically significant.

7.5 Documentation of Adverse Events

All AEs must be captured in the source documents, as well as reported in *electronic document capture (EDC) system*. AEs reported using SAE forms must also be reported in *EDC system*.

All serious and non-serious AEs occurring from the start of study medication administration to the end of study drug administration visit must be recorded as AEs on the CRF. The Investigator should review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported.

7.6 Follow-Up of AEs and SAEs

All SAEs and AEs should be followed until 4 weeks after the last dosing of study drug/biologic or until they are resolved (return to normal or baseline values), stabilized, improve to < Grade 2, or the subject is lost to follow-up and cannot be contacted. Additional investigations (*e.g.*, laboratory tests, diagnostic procedures, or consultation with other healthcare professionals) may be required to completely investigate the nature and/or causality of an AE or SAE. If the subject dies during the study or within 4 weeks following the last dose of study medication, any postmortem findings (including histopathology) should be provided to the Sponsor.

After the Off Treatment Visit, only AEs considered related to study drug are to be followed until resolution (return to normal or baseline values), stabilized, improve to < Grade 2, patient starts another treatment, or the subject is lost to follow-up and cannot be contacted.

CRF data should be updated with any new information as appropriate.

7.7 Pregnancy

If the study subject is the father, then two forms should be completed, one for the father and the other for the mother and neonate. To ensure subject safety each pregnancy must also be reported to Merck within 15 days of learning of its occurrence.
Pregnancies and lactations that occur in a study subject or in a study subject's partner from the time of treatment allocation through 120 days following cessation of study treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator to the Central Office within 24 hours or learning of the event. Central Office will report pregnancy to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) within 2 working days. All reported pregnancies must be followed up to determine outcome, including

spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

7.8 Investigator Notifications

The Sponsor-Investigator will receive Investigator Notifications (INs) issued by Merck for suspect, unexpected SAEs which have occurred in Merck-sponsored studies with the study drug. The Sponsor-Investigator is responsible for forwarding these INs to all sub-investigators participating in the study, as well as to the Research Ethics Boards, according to local practice.

7.9 Data Safety and Monitoring Board

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study to see if there are unexpected or more serious side effects than described in the consent. For this study, the Drug Development Program DSMB will be fulfilling this role.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 Investigational Agent - Pembrolizumab

Pembrolizumab will be provided by Merck as a liquid solution (100 mg/4mL vial) in Type I glass vials intended for single use only. The drug product is stored under refrigerated conditions (2 to 8°C).

The liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. Refer to pharmacy manual for more information.

Pembrolizumab Manufacturing

Merck manufactures Pembrolizumab for clinical use.

Pembrolizumab Packaging and Labeling

Clinical supplies of pembrolizumab will be affixed with a clinical label in accordance with regulatory requirements.

Pembrolizumab Handling and Storage

Investigational agent will be stored under secure (with limited access), and temperature-controlled conditions specified on the label for the duration of the study. Receipt and dispensing of trial medication

must be recorded by an authorized person at the trial site.

Pembrolizumab Ordering and Shipping

Pembrolizumab will be supplied by Merck to the study site. The Principal Investigator, or authorized study personnel, upon receipt of the study medication supplies, will conduct an inventory and acknowledge receipt to Merck, or designee.

Study medication should only be dispensed once a subject has (1) signed an informed consent form (ICF), (2) met all eligibility criteria for entry into the study, (3) completed all screening and continuing eligibility requirements, and (4) been assigned a subject identification number.

Agent Accountability
The Investigator is responsible for study medication accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study personnel must maintain study medication accountability records throughout the study.

The accountability records maintained during the study will be used to support subject dosing data. Site personnel are responsible for reconciling and resolving discrepancies in study medication accountability.

Missing study medication must be recorded along with an explanation of the discrepancy. At the conclusion of the study, all unused study medication and all medication containers will be destroyed locally as per UHN destruction policy.

Agent Inventory Records
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received using their site-specific Drug Accountability Record Form (DARF).

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Biomarker analyses in this study will be exploratory.

9.1 Tumor Biopsies

A pre-treatment biopsy will be performed in all patients enrolled. The biopsy should be performed at any time during the screening period before cycle 1, day 1 once informed consent has been signed. The biopsy will be conducted according to institutional guidelines using standard surgical techniques. 4 cores will be obtained.

Tumor material will be prioritized as follows:

1. Whole exome sequencing
2. Whole transcriptome sequencing
3. PD-L1 expression and TIL analysis
4. Methylation profiling

*In the event that a patient has not had a biopsy to determine clinical diagnosis prior to study entry the first core must be prioritized for this. This will require a review by a pathologist of collected samples.

An optional post treatment biopsy will take place between weeks 3-6 and tissue will be banked.

9.1.1 MOLECULAR ANALYSES AND DATA EVALUATION

9.1.1.1 **WES of Tumor DNA**

WES of tumor DNA and germline DNA will be performed in OICR with already established protocol using next generation DNA sequencing. Data generated will be analyzed using established bioinformatics pipelines to study somatic mutations and derive potential mutational signatures. These results should be available within 8 weeks of baseline fresh tumor biopsy.

Germline mutations detected in study subjects will be reported to the co-investigator (treating physician) to facilitate clinical confirmation of mutation(s). Participants with pathogenic germ line mutations identified through the study and who have consented to be informed of genetic information will be approached by the study genetic counselor (Canadian and American board certified). The research results disclosure session will consist of genetic counseling about the research finding and need for confirmation testing. The session will also summarize gene specific risks and inheritance pattern. The study genetic counselor will offer confirmation testing of the research finding through a clinically accredited laboratory. When clinical confirmation results are available, these will be disclosed to the participant and their treating physician by the genetic counselor. Clinical results disclosure session will summarize gene specific cancer risks, inheritance, surveillance for early detection and/or surgical interventions for prevention, and procedures for testing family members.

9.1.1.2 **RNAseq of Tumor**

Whole transcriptome sequencing of tumor RNA will be performed using next generation sequencing in OICR with established protocols (see Lab Manual). RNAseq data will be used to perform exploratory analysis. Planned analyses include evaluation of differences in gene expression levels between responders and non-responders to study treatment. Further exploratory analyses will include interrogation of inflammatory signatures. In patients consenting for a second optional biopsy, immune signatures will be compared pre and post treatment.

9.1.2 **PD-L1 and Immunoscore**

Tumor samples from this study will be analyzed for percentage PD-L1 expression. PD-L1 protein level, as assessed by IHC in tumor sections, has been shown to correlate with response to pembrolizumab in subjects with NSCLC, and a PD-L1 IHC diagnostic is marketed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (i.e., triple-negative breast cancer, head and neck, and gastric). The burden of tumor-infiltrating lymphocytes (TILs) may also predict response to ICIs and provide an ‘immunoscore’ which can prognosticate in HCC; densities of CD8, CD3, CD45R0 and PD-1 will also be assessed.[65,66] This will be performed by QualTek Molecular Laboratories, Pennsylvania.

9.1.3 **Methylation Profiling**

DNA extracted from tumor biopsies will be delivered to the DeCarvalho laboratory at the Princess Margaret Cancer Centre for DNA methylation mapping. Tumor methylation profiling will be correlated with that seen in cfDNA. (Section 9.2.1)

9.1.4 **Handling of specimens**

See lab manual.

9.2 Blood withdrawal and biomarker studies

9.2.1 **ctDNA**

There is evidence that ctDNA obtained from blood specimens of advanced cancer patients may be representative of the mutational status of DNA from tumor cells and may identify the emergence of treatment resistance prior to radiographic progression.[67] 2 X 10 ml EDTA will be drawn on days 1, cycle 1 day 10+/- 2 days and cycle 5, day 1 (day 85) +/- 7days. A further sample will be collected at progression. Whole blood samples should be processed (double spun) within 4 hours of collection to separate cells from plasma. Plasma Serum samples will be stored at -80°C until batched transfer to biospecimens program. Cell free DNA will be analyzed for circulating tumour DNA quantitative analysis. This testing will be performed by the Pugh lab at OICR.

9.2.2 **Germline analysis**

Blood draw at C1D1 will also be used to obtain a buffy coat for DNA extraction and germline analysis. Sample should be transferred to OICR and stored at -80ºC for further processing.

9.2.3 **Methylation profiling**

Plasma separated from samples at time-points in 9.2.1 will also be used for DNA methylation profiling. 1ml of plasma will be delivered to the DeCarvalho laboratory. Methods to be described in laboratory manual.

9.2.4 **Cytokine analysis**

1 x 10ml EDTA sample will be collected Cycle 1, Day 1, Cycle 1 Day 5, Cycle 1 Day 10+/-2, Cycle 3 Day 1, Cycle 5 Day 1 and at progression (+/- 7 days). Whole blood samples should be processed (double spun) within 4 hours of collection to separate cells from plasma. Plasma Serum samples will be stored at -80◦C until batched transfer to biospecimens program. Expression of clinically relevant cytokines will be measured using a multiplexed electrochemiluminesce (ECL) immunoassay manufactured by Meso Scale Diagnostics, and performed at the Liu lab at the University Health Network. We will specifically look for cytokines reflective of an abscopal effect.

10. STUDY CALENDAR

Baseline (pre-study) evaluations are to be conducted within 14 days prior to start of protocol therapy, unless specified differently in the study calendar. Scans (including tumor measurements) x-rays, informed consent, tumor biopsy, and hepatitis testing must be done ≤ 28 days prior to the start of therapy. In the event that the subject's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Some visits might be conducted remotely and / or some assessments might be deferred as per physician discretion. Some of the safety lab assessments may also be done at external or community laboratories as applicable. In such cases, sites should provide Normal reference ranges of such lab and lab licenses to the Central Office.

The following schedule of assessments applies to all subjects. More frequent assessments should be obtained if clinically indicated. If pre-study laboratory and clinical assessments were done within 5 days prior to treatment initiation, they do not need to be repeated for cycle 1 day 1. For subsequent cycles 2+, day 1 assessments can be completed up to 4 days prior to day 1. A cycle is 21 days long for the purposes of this protocol.

		Cycle 1				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6+**		
	Pre-Study	**Day 1**	**Day 2**	**Day 5**	**Day 10**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Off Treatment Visit[c]**	**Survival Follow-Up[c]**
Pembrolizumab		A				A	A	A	A	A		
SBRT			B----------B									
Informed consent (Main and Optional)	X											
Demographics	X											
Medical history	X											
TNM Staging, BCLC Staging	X											
Vascular Thrombosis Staging[f]	X											
Concurrent meds	X	X----------X										
Physical exam	X	X		X[e]		X	X	X	X	X	X	
Vital signs[d]	X	X	X	X[e]		X	X	X	X	X	X	
Height	X											
Weight	X	X				X	X	X	X	X	X	
Performance status	X	X	X			X	X	X	X	X	X	
Child-Pugh Score	X	X		X[e]		X	X	X	X	X	X	
ALBI Score	X	X		X		X	X	X	X	X	X	
CBC w/diff, PT/INR	X	X		X[e]		X	X	X	X	X	X	
Neutrophil-Lymphocyte Ratio	X	X		X		X	X	X	X	X	X	
Serum chemistry[a]	X	X		X[e]		X	X	X	X	X	X	
T3 and TSH	X	X					X		X			
Hepatitis B Testing[g]	X											
Hepatitis C Testing[h]	X											

Anti-HDV Testing[j]	X											
ECHO	X			As clinically indicated								
EKG	X			As clinically indicated								
Adverse event evaluation				X----------							X	
Tumor measurements	X			X^m Documentation (radiologic) must be provided for subjects removed from treatment for progressive disease.							X^i	
Radiologic evaluation	X			X^m							X^i	
B-HCG	X^b											
AFP	X	X				X	X	X	X	X	X	
Biopsy for correlative studies	X											
Optional biopsy for correlative studies						X^k						
Blood for ctDNA/methylation[l]		X			X				X		X	
Blood for cytokine analysis[l]		X		X	X		X		X		X	
Survival status												X

All assessments may be performed up to 2 working days prior to scheduled day.

A: Pembrolizumab 200 mg IV Q3W

B: SBRT as per Section 5.1.2, commencing Cycle 1 Day 2, consisting of 5 fractions over 5-15 days

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.

b: Serum pregnancy test (women of childbearing potential).

c: See Section 5.4 for post-treatment follow-up requirements.

d: Blood pressure, temperature, pulse, O2 saturation, and respiratory rate.

e: Day of assessment while on SBRT may vary due to weekends, but should be as close to day 3 as possible.

f: See Appendix 4 for vascular thrombosis staging chart.

g: All patients should have baseline Hepatitis B screening which should include: HbsAg, Anti-Hbs and Anti-Hbc (total+IgM). For patients with known hepatitis B, or if they have been deemed infected through baseline screening, additional test should include: HBV viral load (DNA), HbeAg and Anti-Hbe. If HBV viral load has been performed within previous 3 months a repeat test is not required. If Hepatitis B Testing has been performed for eligibility less than 28 days prior to start of therapy it is not required to be repeated again as a part of Baseline (Pre-study) evaluations.

h: All patients should have baseline Hepatitis C screening which should include: Anti-HCV. For patients with known hepatitis C, or if they have been deemed infected through baseline screening, HCV viral load (RNA) should be performed. If HCV viral load has been performed within previous 3 months a repeat test is not required. If Hepatitis C Testing has been performed for eligibility less than 28 days prior to start of therapy it is not required to be repeated again as a part of Baseline (Pre-study) evaluations.

i: Patients who come off study treatment for reasons other than radiological progression are to have tumor measurements and disease response evaluated ever 3mo ± 14 days until documented progression per iRECIST or start of new therapy.

j: Only required if the patient has a known history of Hepatitis B and the testing has not been completed previously. If testing has been done previously, a repeat test is not required. If Anti-HDV Testing is required, this must be done ≤ 28 days prior to the start of therapy.

k: Optional biopsy to be done between 3-6 weeks on study for patients that have consented to procedure

l: Research bloods to be drawn prior to Pembrolizumab administration. Research blood must be collected on-site at Princess Margaret Cancer Centre.

m: Radiologic evaluation and tumor measurements should be performed at 12 weeks on treatment and then repeated every 10 weeks thereafter (± 2 weeks). CT scans should be performed at planned time points regardless of any dose delays.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, subjects should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-8 weeks following initial documentation of objective response.

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

Response and progression will be evaluated in this study using both RECIST 1.1 and the new criteria proposed by immune modified Response Evaluation Criteria in Solid Tumors (iRECIST) guideline (Seymor 2017). Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the iRECIST criteria. Overall response will be assessed, as well as response in lesions outside the SBRT treatment field. These criteria keep the uni-dimensional measurement of RECIST, but incorporate the concept of unconfirmed progression (iUPD) noted with the use of immunotherapy. In the case of new lesions, assessments continue as per RECIST 1.1 but are recorded in a separate case report form. Contrasting to RECIST 1.1 new lesions may results in iUPD but immune confirmed progression (iCPD) is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD. iUPD may occur before iPR, iCR or iSD, in contrast to RECIST 1.1 where progression could not occur. Notable in this study, radiated lesions will be counted as part of the response criteria, an exception to the rules of RECIST 1.1.

11.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with pembrolizumab.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective definitive disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions. For

iUPD, iCPD will need to be confirmed by repeat imaging 4-8 weeks after iUPD was identified, as per iRECIST.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. For nodal lesions, see criteria below. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Tumor lesions treated with SBRT as part of the study protocol will be considered measurable for the primary analysis. Other previously irradiated lesions will not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Vascular thrombosis will be considered non-measurable disease, unless vascular HCC is the only HCC present. In this case, vascular response guidelines in 11.1.4.3 should be used.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Vascular thrombi will not be selected as target lesions, unless vascular HCC is the only HCC present. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the

measurable dimension of the disease. Radiated lesions can be counted as target lesions provided there has been demonstrated progression in the lesion.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT & MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT should be performed with slice thickness of 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

11.1.4 RECIST/ iRECIST Assessment of Disease

Response

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis reduction to < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [ref RECIST 1.1]) before CR can be accepted. Confirmation of response is required

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Patients with CR/iCR or PR/iPR should have scans repeated after 4 weeks, but no more than 8 weeks, to confirm response.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). When the patient has only non-measurable disease, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Patients that are clinically well may continue on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of PD by immune response criteria *[Seymour 2017]*. In this situation, patients do not have unequivocal progression until immune response criteria are met (see Table 10 below).

Table 10: Integration of Target, non-Target and New Lesions into Response Assessment

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes*	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, tumour nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR / non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

* Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see New Lesion section below.

Immune-Related Response Assessment (iRECIST)

Overall response will also be assessed using iRECIST *[Seymour 2017]*. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-points and best overall responses will be recorded separately.

Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in **Table 11**, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form.

New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per organ, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the

measurements of NLT should not be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD, confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table 11: Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirm iCPD if NLs were previously identified and have increased in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD, iPR, iCR	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD or iCR	No	iUPD	Remains iUPD unless iCPD confirmed based on: - further increase in SOM by at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified target lesion iUPD SOM ≥5 mm **and / or** - NT lesion iUPD (prior assessment need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD ≥5 mm **and / or** - previously identified NT lesion iUPD (need not be unequivocal) **and /or** - size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on - increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no pseudoprogression (PSPD) occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.
** In any lesion category.
*** Previously identified in assessment immediately prior to this time point.

Vascular Thrombosis Response Evaluation

There are no validated guidelines to monitor and report vascular thrombosis response. Consistent with RECIST1.1, thrombosis will be considered non-measurable disease. Vascular thrombosis response should be recorded using the following guidelines:

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

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

iPD thrombosis: any unequivocal, unambiguous increase in the volume of new or existing enhancing thrombosis

Note that for "unequivocal progression" of thrombosis (non-measurable disease), the increase in overall tumor burden (enhancing thrombosis) must be comparable to the increase required for iRECIST definition of PD of measurable disease.

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

11.1.5 Progression-Free Survival

Progression free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.6 Response Review

All iCR and iPR responses will be reviewed by an expert(s) independent of the study at the subject's completion of the study by simultaneous review of subject files and radiologic images.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 above (Adverse Events: List and Reporting Requirements).

12.1 Data Collection and Reporting

All data obtained in the clinical trial described in this protocol will be reported on eCRFs in the Medidata Electronic Document Capture system (Medidata). Data reported on eCRFs should be consistent with the source documents and verifiable. All data for the primary and secondary endpoints will source verified prior to publication. The Investigator will review the data and electronically sign the eCRFs to acknowledge agreement with the data entered. Data will be entered into Medidata will be used for developing tables and listings for the final study report.

Prior to the start of the study, the Investigator will complete a Site Participants Log showing the signatures and handwritten initials of all individuals who are authorized to make or change entries on source documents and eCRFs.

12.2 Source Documents

Source documents refer to the original documents, data, and records where the first recording of a data point occurred. Examples of source documentation include, but are not limited to:

Hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)

Please ensure that source document entries are attributable, legible, contemporaneous, original, and accurate. Note that sign-off of source documents should be attributable to a single record and "bracketing" multiple entries on source document pages for a single signature is not allowed. Corrections to source document entries should only be completed by drawing a single line through the previous entry and then recording the corrected data, initialing the change, and dating the change. Only the individual that initially recorded the data should make any corrections.

12.3 Retention of Subject Records and Study Files

The ICH guidance document, Good Clinical Practice: Consolidated Guidelines (ICH Guidance Document E6) (1997) states that the investigator and sponsor shall retain study records relating to the study until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In the event of a trial discontinuation, sponsor records should also be kept for a minimum of 2 years. Per Health Canada, all original records should be maintained for 25 years after the above requirements are satisfied and the final report has been issued. Records contained in the Clinical Trial Application should be maintained on file for at least 25 years. We will comply with these regulations. The Sponsor will notify sites when documents are to be destroyed.

12.4 Site and Study Closure

Upon completion of the study, the following activities, when applicable, will be completed by the Central Office in conjunction with the Investigator, as appropriate:

- Collection of study materials (i.e., specimen collection kits, drug shippers, etc.)
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused study medication
- Review of site study records for completeness

If the Sponsor or Investigator or appropriate regulatory officials identify conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information to the Sponsor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements
- Refusal of the Investigator to supply source documentation of work performed in this clinical trial

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonisation (ICH) sixth efficacy publication (E6) on Good Clinical Practice, ICH E6 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a single-arm, non-comparative, open-label phase II study of combination treatment with pembrolizumab and SBRT in patients with advanced HCC who have experienced disease progression after treatment with sorafenib/lenvatinib.

Study objectives are stated in Section 1.1 to 1.3.

The primary endpoint of the study is overall response rate, defined as the proportion of the subjects in the study population who have a complete response (iCR) or partial response (iPR), as defined by iRECIST, at any time on study treatment. Of note this may follow a period of iUPD.

13.2 Sample Size/Accrual Rate

Given the preliminary results with nivolumab, we would expect that pembrolizumab alone would produce responses in 15% of patients.[24] We hypothesize that combining pembrolizumab with SBRT will increase the ORR to 40%, a clinically meaningful increase in systemic response rate and indicative of significant activity (Note: ORR is a composite sum of irradiated local tumor and other measurable metastatic disease - local radiotherapy response, systemic pembrolizumab response and potential abscopal effect on all measurable disease).

With 90% power, we would need to accrue 22 evaluable patients in a two-stage study design, with a one-sided significance level of 10%. If 2 or more patients show response from the first 10 evaluable patients, we will continue to accrue to a total of 22 evaluable patients. We expect to accrue up to 27 patients as some patients may not be evaluable for the primary endpoint. A total number of 6 or more responders in 22 evaluable patients would be considered to reject the null hypothesis. We expect to accrue 2-3 patients per month, leading to complete accrual in 12 months following study activation.

13.3 Analysis of Primary Endpoint

Overall Response Rate (ORR)
ORR is defined as the proportion of the subjects in the study population who have a complete response (iCR) or partial response (iPR), as defined by iRECIST, at any time on study treatment. This is noting that radiated lesions will count as target lesions provided there has been demonstrated progression in the lesion.

The point estimate and 95% confidence interval for ORR will be provided using the Clopper and Pearson exact binomial method. An interim analysis for futility will be undertaken when response data are available on the first 10 evaluable subjects enrolled. If ≤1 responses are documented, the trial will be stopped. If 2 or more responses (iCR or iPR) are documented, the study will continue to full accrual. Subjects who are inevaluable for the primary endpoint will be replaced.

13.4 Analysis of Secondary Endpoints

Response in non-irradiated lesions
Response in non-irradiated lesions is defined as the proportion of subjects in the study population who demonstrate iCR or iPR, by iRECIST 1.1, when tumors within the radiotherapy treatment field are excluded from analysis. Subjects will be ineligible for this analysis if no RECIST-measurable lesions exist outside the radiotherapy treatment field.

The point estimate and 95% confidence interval for ORR will be provided using the Clopper and Pearson exact binomial method.

Duration of Response (DOR)

For subjects who demonstrate iCR or iPR, by iRECIST, DOR is defined as the time from first documented evidence of iCR or iPR until disease progression or death due to any cause, whichever occurs first.

DOR will be estimated by the Kaplan-Meier method, and the Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with DOR.

Progression-Free Survival (PFS)

PFS is defined as the time from enrollment until the date of objective disease progression, by iRECIST, or death (by any cause in the absence of progression).

PFS will be estimated by the Kaplan-Meier method, and the Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with PFS.

Overall Survival (OS)

OS is defined as the time from study enrollment to death due to any cause.
OS will be estimated by the Kaplan-Meier method, and the Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS.

13.5 Analysis of Exploratory Endpoints

Genomic signatures that may predict responses to Pembrolizumab and radiation will be explored using logistic regression. Descriptive statistics such as mean, standard deviation, median and range, will be reported for the levels of circulation tumor DNA and immunologic correlatives. Comparison between different time points can be made by t-test or Wilcoxon test where appropriate. Logistic regression will be carried out to examine their association with response to pembrolizumab and SBRT.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with pembrolizumab. Toxicities will be evaluated and graded according to CTCAE v4.0, and will be assigned an attribution as per Section 7.2. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests and vital signs.

Toxicity tables will be constructed to summarize the observed incidence of adverse events by toxicity and grade. The relative frequency of each type of toxicity will be quantified as the number of toxicity-evaluable cycles in which the adverse event was noted as grade 3 or higher considered by the treating physician to be possibly, probably or definitely related to one of the agents in the regimen, divided by the number of toxicity-evaluable cycles administered to patients enrolled on the trial.

13.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each subject will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 8 usually designates the "unknown" status of any type of data in a clinical database.]

All of the subjects who met the eligibility criteria (with the exception of those who received no study medication) will be included in the primary analysis of the response rate. Subjects in response categories 4-7 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of the response rate. For analysis of the primary endpoint, subjects with missing data will be considered non-responders. If data are missing for survival endpoints, subjects will be censored at last assessment.

The analysis population for response in non-irradiated lesions consists of subjects with RECIST-measurable disease outside the radiotherapy treatment field. The analysis population for DOR consists of responders (iPR and iCR).

All conclusions will be based on all eligible subjects. Subanalyses may then be performed on the basis of a subset of subjects, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding subjects from the analysis will be clearly reported. The 95% confidence intervals will also be provided.

REFERENCES

1. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-90, 2008
2. 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 10:25-34, 2009
3. Abou-Alfa GK, Niedzwieski D, Knox JJ, et al: Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC): CALGB 80802 (Alliance). ASCO Meeting Abstracts 34:4003, 2016
4. Llovet JM, Decaens T, Raoul JL, et al: Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 31:3509-16, 2013
5. Zhu AX, Park JO, Ryoo BY, et al: Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 16:859-70, 2015
6. Zhu AX, Kudo M, Assenat E, et al: Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 312:57-67, 2014
7. Bruix J, Merle P, Granito A, et al: Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: results of the international, randomized phase 3 RESORCE trial. Annals of Oncology 27:ii140-ii141, 2016
8. Disis ML: Immune regulation of cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 28:4531-8, 2010
9. Dong H, Strome SE, Salomao DR, et al: Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature medicine 8:793-800, 2002
10. Sharpe AH, Freeman GJ: The B7-CD28 superfamily. Nature reviews. Immunology 2:116-26, 2002
11. Brown JA, Dorfman DM, Ma FR, et al: Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. Journal of immunology 170:1257-66, 2003
12. Francisco LM, Sage PT, Sharpe AH: The PD-1 pathway in tolerance and autoimmunity. Immunological reviews 236:219-42, 2010
13. Talmadge JE, Donkor M, Scholar E: Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer metastasis reviews 26:373-400, 2007
14. Buchbinder EI, Desai A: CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol 39:98-106, 2016
15. Greenwald RJ, Freeman GJ, Sharpe AH: The B7 family revisited. Annual review of immunology 23:515-48, 2005
16. Polcher M, Braun M, Friedrichs N, et al: Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 59:909-19, 2010
17. Kassel R, Cruise MW, Iezzoni JC, et al: Chronically inflamed livers up-regulate expression of inhibitory B7 family members. Hepatology 50:1625-37, 2009
18. Diehl L, Schurich A, Grochtmann R, et al: Tolerogenic maturation of liver sinusoidal endothelial cells promotes B7-homolog 1-dependent CD8+ T cell tolerance. Hepatology 47:296-

305, 2008
19. Yu MC, Chen CH, Liang X, et al: Inhibition of T-cell responses by hepatic stellate cells via B7-H1-mediated T-cell apoptosis in mice. Hepatology 40:1312-21, 2004
20. Zhang G, Li N, Zhang P, et al: PD-1 mRNA expression is associated with clinical and viral profile and PD1 3'-untranslated region polymorphism in patients with chronic HBV infection. Immunol Lett 162:212-6, 2014
21. Gao Q, Wang XY, Qiu SJ, et al: Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 15:971-9, 2009
22. Shi F, Shi M, Zeng Z, et al: PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. Int J Cancer 128:887-96, 2011
23. Morales-Kastresana A, Sanmamed MF, Rodriguez I, et al: Combined immunostimulatory monoclonal antibodies extend survival in an aggressive transgenic hepatocellular carcinoma mouse model. Clinical cancer research : an official journal of the American Association for Cancer Research 19:6151-62, 2013
24. Melero I, Sangro B, Yau T, et al: Safety and preliminary efficacy of of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (aHCC): Interim analysis of the phase ½ Checkmate-040 study. Proc ESMO 2016.25. Blomgren H, Lax I, Naslund 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 34:861-70, 1995
26. Mendez Romero A, Wunderink W, Hussain SM, et al: Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase i-ii study. Acta Oncol 45:831-7, 2006
27. Cardenes HR, Price TR, Perkins SM, et al: Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol 12:218-25, 2010
28. Kwon JH, Bae SH, Kim JY, et al: Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. BMC Cancer 10:475, 2010
29. Seo YS, Kim MS, Yoo SY, et al: Preliminary result of stereotactic body radiotherapy as a local salvage treatment for inoperable hepatocellular carcinoma. J Surg Oncol 102:209-14, 2010
30. Louis C, Dewas S, Mirabel X, et al: Stereotactic radiotherapy of hepatocellular carcinoma: preliminary results. Technol Cancer Res Treat 9:479-87, 2010
31. Son SH, Choi BO, Ryu MR, et al: Stereotactic body radiotherapy for patients with unresectable primary hepatocellular carcinoma: dose-volumetric parameters predicting the hepatic complication. Int J Radiat Oncol Biol Phys 78:1073-80, 2010
32. Sanuki N, Takeda A, Oku Y, et al: Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. Acta Oncol 53:399-404, 2014
33. Honda Y, Kimura T, Aikata H, et al: Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. J Gastroenterol Hepatol 28:530-6, 2013
34. Bujold A, Massey CA, Kim JJ, et al: Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 31:1631-9, 2013
35. Xi M, Zhang L, Zhao L, et al: Effectiveness of stereotactic body radiotherapy for

hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. PLoS One 8:e63864, 2013
36. Dawson LA, Eccles C, Craig T: Individualized image guided iso-NTCP based liver cancer SBRT. Acta Oncol 45:856-64, 2006
37. Velec M, Craig T, Wang L, et al: Predictors of Liver Toxicity Following Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma. International Journal of Radiation Oncology • Biology • Physics 93:E175
38. Kwilas AR, Donahue RN, Bernstein MB, et al: In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. Front Oncol 2:104, 2012
39. Twyman-Saint Victor C, Rech AJ, Maity A, et al: Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 520:373-7, 2015
40. Hiniker SMea: A prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. International Journal of Radiation Oncology • Biology • Physics , Volume 93 , Issue 3 , S95
41. Schaue D, Ratikan JA, Iwamoto KS, et al: Maximizing tumor immunity with fractionated radiation. Int J Radiat Oncol Biol Phys 83:1306-10, 2012
42. Finkelstein SE, Timmerman R, McBride WH, et al: The confluence of stereotactic ablative radiotherapy and tumor immunology. Clin Dev Immunol 2011:439752, 2011
43. 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 15:5379-88, 2009
44. Ohba K, Omagari K, Nakamura T, et al: Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. Gut 43:575-7, 1998
45. Nam SW, Han JY, Kim JI, et al: Spontaneous regression of a large hepatocellular carcinoma with skull metastasis. J Gastroenterol Hepatol 20:488-92, 2005
46. Nakanishi M, Chuma M, Hige S, et al: Abscopal effect on hepatocellular carcinoma. Am J Gastroenterol 103:1320-1, 2008
47. Okuma K, Yamashita H, Niibe Y, et al: Abscopal effect of radiation on lung metastases of hepatocellular carcinoma: a case report. J Med Case Rep 5:111, 2011
48. Friedman D, Baird JR, Young KH, et al: Programmed cell death-1 blockade enhances response to stereotactic radiation in an orthotopic murine model of hepatocellular carcinoma. Hepatol Res, 2016
49. Park SS, Dong H, Liu X, et al: PD-1 Restrains Radiotherapy-Induced Abscopal Effect. Cancer Immunol Res 3:610-9, 2015
50. Postow MA, Callahan MK, Barker CA, et al: Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 366:925-31, 2012
51. Hiniker SM, Chen DS, Reddy S, et al: A systemic complete response of metastatic melanoma to local radiation and immunotherapy. Transl Oncol 5:404-7, 2012
52. 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 1:365-72, 2013
53. Stamell EF, Wolchok JD, Gnjatic S, et al: The abscopal effect associated with a systemic anti-melanoma immune response. Int J Radiat Oncol Biol Phys 85:293-5, 2013
54. Karbach J, Gnjatic S, Biskamp M, et al: Long-term complete remission following radiosurgery and immunotherapy in a melanoma patient with brain metastasis: immunologic

correlates. Cancer Immunol Res 2:404-9, 2014
55. Bernstein MB, Krishnan S, Hodge JW, et al: Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol 13:516-24, 2016
56. Zeng J, See AP, Phallen J, et al: Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. Int J Radiat Oncol Biol Phys 86:343-9, 2013
57. Theurich S, Rothschild SI, Hoffmann M, et al: Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma. Cancer immunology research 4:744-54, 2016
58. Kwon ED, Drake CG, Scher HI, et al: Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 15:700-12, 2014
59. Tang C, Welsh JW, de Groot P, et al: Ipilimumab with stereotactic ablative radiation therapy: Phase I results and immunologic correlates from peripheral T-cells. Clinical cancer research : an official journal of the American Association for Cancer Research, 2016
60. Hiniker SM, Reddy SA, Maecker HT, et al: A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. Int J Radiat Oncol Biol Phys 96:578-88, 2016
61. Seymour L, Ivy SP, Sargent D, et al: The Design of Phase II Clinical Trials Testing Cancer Therapeutics: Consensus Recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. American Association for Cancer Research 16:1764-1769, 2010
62. Ribas A: J Clin Oncol 33, 2015 (suppl; abstr 3001)
63. al Re: Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. . Journal of Clinical Oncology, 2015 ASCO Annual Meeting (May 29 - June 2, 2015).
Vol 33, No 15_suppl (May 20 Supplement), 2015: 3001
64. Ono A, Fujimoto A, Yamamoto Y, et al: Circulating Tumor DNA Analysis for Liver Cancers and Its Usefulness as a Liquid Biopsy. Cellular and Molecular Gastroenterology and Hepatology 1:516-534, 2015
65. Gabrielson A, Wu Y, Wang H, et al: Intratumoral CD3 and CD8 T-cell Densities Associated with Relapse-Free Survival in HCC. Cancer Immunol Res 4:419-30, 2016
66. Sun C, Xu J, Song J, et al: The predictive value of centre tumour CD8(+) T cells in patients with hepatocellular carcinoma: comparison with Immunoscore. Oncotarget 6:35602-15, 2015
67. Misale S, Yaeger R, Hobor S, et al: Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature 486:532-6, 2012

APPENDIX 1 PERFORMANCE STATUS CRITERIA

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

APPENDIX 2 CHILD-PUGH SCORE

The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although originally designed to predict mortality after surgery, it is now used to determine prognosis and eligibility for treatment as well as the need for future liver transplantation.

The score employs five clinical measures of liver disease. Each measure is scored between 1 and 3, with 3 indicating most severe derangement. The scores are then added to form a total.

Measure	**1 point**	**2 points**	**3 points**
Bilirubin (umol/L)	<34	34-51	>51
Albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Easily controlled	Poorly controlled
Hepatic encephalopathy[1]	None	Grade I-II (mild or moderate)	Grade III-IV (severe or coma)

Points	**Class**	**One year survival**	**Two year survival**
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

[1] Hepatic encephalopathy graded according to West Haven Criteria for Semi-quantitative Grading of Mental Status: *Adapted from: Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins; 1979.*

- Grade I: Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade II: Lethargy or Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior
- Grade III: Somnolence to semi-stupor, but responsive to verbal stimuli
  Confusion; Gross disorientation
- Grade IV: Coma (unresponsive to verbal or noxious stimuli)

APPENDIX 3 HEPATITIS B DEFINITIONS AND TREATMENT CONSIDERATIONS

The following table describes the various definitions for hepatitis B and the treatment conditions for subjects with hepatitis B.

Hepatitis B Definitions and Treatment Considerations

Test	Patient Status	Eligible for trial?	HBV treatment indicated?
HBsAg (-) Total anti-HBc (+) HBsAb (+)	Immune after infection	Yes	No
HBsAg (-) Total anti-HBc (-) HBsAb (+)	Immune after vaccination	Yes	No
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (+) HBsAb (-)	Acute Infection	No	N/A
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (-) HBsAb (-)	Chronic Infection	Yes	Yes, need HBV treatment for ≥ 2 weeks prior to start of pembrolizumab Exclude if: (a) <2 weeks of therapy; (b) HBV viral load not under control during this time frame (c) Documented HBV flare in the past 12 weeks
HBsAg (-) Total anti-HBc (+) IgM anti-HBc (-) HBsAb (-) HBV viral load (-)	Unclear. Could be: (1) Resolved infection (2) False positive anti-HBc (3) Low level infection (4) Resolving acute infection	Yes	No
HBsAg (-) Total anti-HBc (+) IgM anti-HBc (-) HBsAb (-) HBV viral load (+)	(1) Low level infection (2) Resolving acute infection	Yes	Yes (as for acute infection)

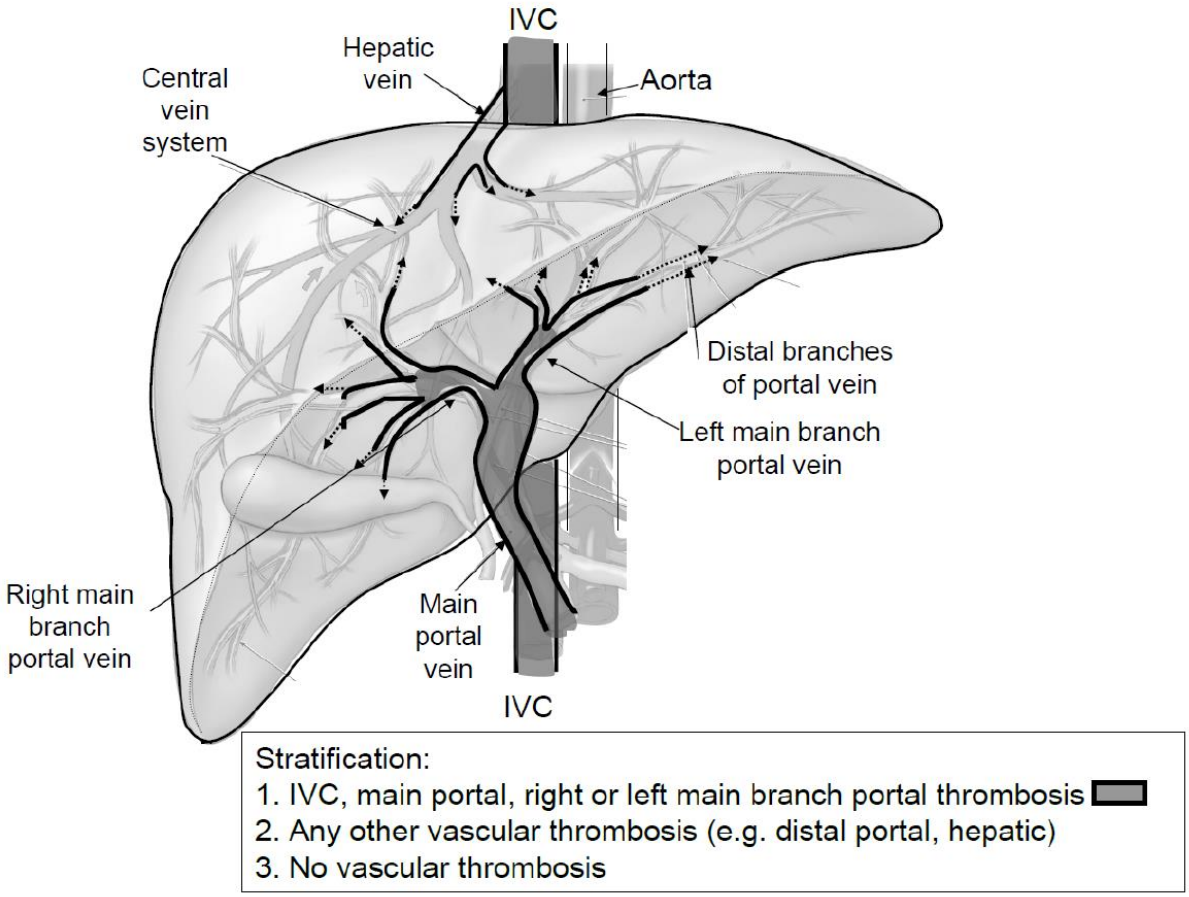
APPENDIX 4 VASCULAR THROMBOSIS STAGING

The three categories for staging vascular tumor thrombus are:

1. Tumor thrombosis involving the IVC, the main portal vein or the right or left main branch portal vein. This includes any thrombi involving these vascular structures at least partially, defined as involving any of the IVC, main portal vein or the right or left main branches of the portal vein. The right and left main branches of the portal vein are the first branches off the main portal vein, up to the first bifurcation of the right and left portal veins, as shown in the diagram below.

2. Any other thrombosis (e.g. involving the more distal portal veins or hepatic veins).

3. No vascular thrombosis.



APPENDIX 5 DATA MANAGEMENT GUIDELINES

Data Management Guidelines

Case Report Form Submission Schedule

The Registration Checklist will be a paper form that will be provided by the Drug Development Central Office. All other data required for the study will be collected in eCRFs in Medidata. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Eligibility Checklist	At the time of registration
Baseline Form	Within 4 weeks of on study date
On Treatment Form	Within 4 weeks of the end of each cycle of treatment
Off Treatment Form	Within 4 weeks of the subject coming off-study
Short Follow-up Form	Within 4 weeks of the subject coming to clinic. Required every 3 months until death.
Final Report Form	Within 3 months of the subject's death being known to the investigator unless this constitutes a reportable adverse event when it should be reported according to expedited guidelines

Case Report Form Completion

The paper Registration Checklist must be completed using black or blue ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction. eCRFs will be completed according to the schedule noted above.

All subject names or other identifying information will be removed prior to being sent to the Central Office and the documents labeled with subject initials, study number and the protocol number if applicable.

Monitoring

This is an investigator initiated study and study monitoring will be performed by the Drug Development Program Central Office or its designate.

Data in the Medidata Rave eCRFs will be monitored on a regular basis and quality assurance measures will be performed. Electronic data queries as well as paper query letters may be issued to the site.

Regulatory Requirements

- Please submit all required documents to the DDP Central Office.
- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking. The signed original is to be sent to the DDP Central Office.

- All investigators must have an up-to-date CV (signed within 2 years) on file with the DDP Central Office.
- Laboratory certification/accreditation and normal ranges are required
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks
- Consent forms must be reviewed by the Central Office before submission to the local ethics regulatory board (REB/IRB) and must include a statement that 1) information will be sent to and 2) medical records will be reviewed by the DDP Central Office.
- A Membership list of the local ethics board is required.
- A copy of the initial approval letter from the ethics board must be submitted to the DDP Central Office.
- A completed Site Participant List/Training Log is required and must be submitted to DDP Central Office
- Continuing approval will be obtained at least yearly until follow-up on subjects is completed and no further data is being obtained for research purposes