PI Pembro in Combination With Stereotactic Body Radiotherapy for Liver Metastatic Colorectal Cancer

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Title: Pembrolizumab in combination with stereotactic body radiotherapy for liver metastatic colorectal cancer

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1.0 TRIAL SUMMARY

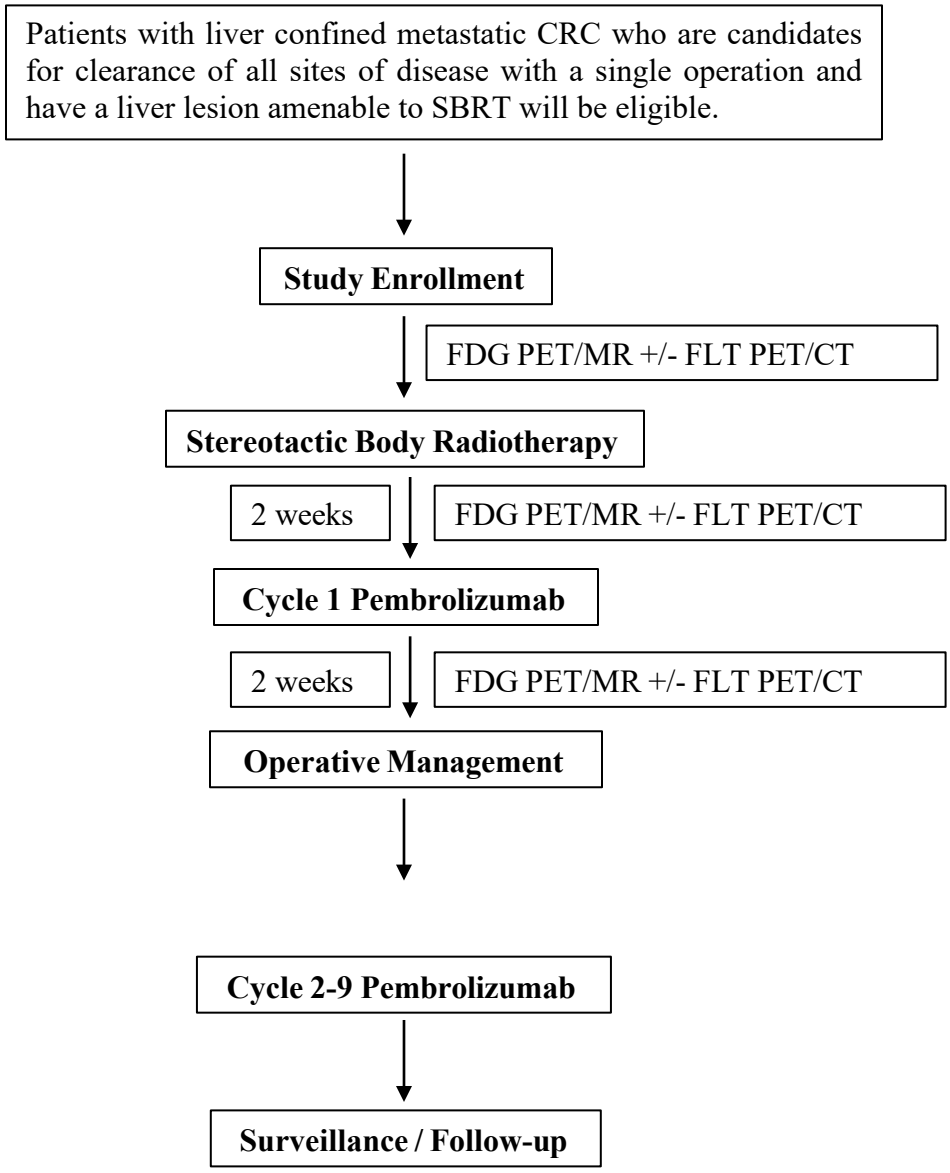
Abbreviated Title	Pembrolizumab and SBRT for liver metastatic CRC
Trial Phase	Phase Ib
Clinical Indication	Oligometastatic CRC to the liver
Trial Type	Investigator Initiated
Type of control	Historic
Route of administration	Intravenously
Trial Blinding	None
Treatment Groups	1
Number of trial subjects	15
Estimated enrollment period	8/2016 to 2/2018
Estimated duration of trial	18 months
Duration of Participation	5 years

2.0 TRIAL DESIGN

2.1 Trial Design

This is a phase 1b feasibility study to evaluate the use of PD-1 blockade in combination with ablative radiotherapy for the treatment of metastatic colorectal cancer (CRC). This study will examine the sequential combination of stereotactic body radiotherapy (SBRT) and pembrolizumab for patients for whom the goal is eradicating all known sites of disease. It is very likely that for many patients the SBRT therapy will be completed following other modalities including operative resection or ablation. The primary endpoint of this study is to examine the safety of radiotherapy to the liver in combination with pembrolizumab. The primary response endpoint will be the rate of cancer recurrence at 1 year following resection of all known sites of disease. Secondary response endpoints will include time to disease recurrence, disease free survival and overall survival. In addition, novel imaging biomarkers including multiparametric elements from PET/MR imaging will be evaluated. The ability to monitor response to immunotherapies remains difficult with standard approaches. Imaging biomarkers based on tumor metabolic activity, texture analysis, and diffusivity will improve noninvasive evaluation of response to immunotherapies. Correlative studies will examine the induction of a local immune response in excised liver tumors as indicated by intra-tumoral lymphocyte infiltration, and also PDL-1 expression comparing pretreatment tissue samples to resected specimens.

2.2 Trial Diagram



A total of 15 patients will be enrolled.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objectives

(1) To determine the safety and tolerability of pembrolizumab in combination with SBRT to the liver.

(2) To determine the recurrence rate at 1 year following clearance of metastatic disease in the setting of treatment with SBRT and pembrolizumab.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) To evaluate time to recurrence, disease free survival and overall survival in these patients.

3.3 Exploratory Objectives

(1) To evaluate novel imaging biomarkers using PET/MR to potentially improve noninvasive determination of response to therapy.

(2) To determine if ablative radiotherapy in combination with pembrolizumab is able to induce an immune response in CRC tumors indicated by an increase in tumor-infiltrating lymphocytes.

(3) To investigate expression levels of PDL1 in CRC liver metastases following treatment with SBRT and pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. 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 (encoded by the gene Pdcd1) 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). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig

Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. 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. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs 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. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region

and contain short cytoplasmic regions with no known signaling motifs. 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. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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 patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Colorectal cancer (CRC) is a common disease and the second leading cause of cancer related death in the United States. It is one of the few cancers in which aggressive local approaches to treat systemic metastases have resulted in clinical benefit. Despite these approaches CRC remains a deadly disease and better treatment options are clearly needed. Approximately 70-80% of patients with resectable metastatic disease will have disease recurrence following potentially curative treatment. The one-year recurrence rate for this population is ~40-50% and another 15% of patients recur within the second year. Subtypes of CRC are associated with robust populations of tumor infiltrating lymphocytes, mainly those with microsatellite instability. Immunotherapy for multiple cancer types has been an area of significant interest over the past few years, including the use of anti-PD1 antibodies. Investigations are currently underway examining these therapies in these populations and other studies have demonstrated benefit from PD1-directed therapies in patients with metastatic CRC.

In order to optimize the response of immunotherapeutics to microsatellite stable CRC it will be beneficial to use these agents in conjunction with a means to enhance tumor antigen presentation and co-stimulation, and in a clinical setting where sufficient time exists to allow for immune-based therapies to have their effects. Previous studies have not focused on CRC as a highly immunogenic cancer and therefore adjunctive therapies might be especially important to enhance the effect of these therapies for the treatment of microsatellite stable CRC. Stereotactic body radiation therapy (SBRT) is commonly utilized to treat liver metastatic CRC. This method uses very high doses of focused radiation to ablate tumors. This causes localized inflammation, a potential increase in immunogenic intra-tumoral and intra-lymphatic antigen release, and a rapid influx of responding immune cells. We hypothesize that radiotherapy-induced tumor necrosis

will enhance the immunogenicity of CRC; moreover, we hypothesize that this enhanced immunogenicity will potentiate the effectiveness of PD-1 blockade for patients.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. 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) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 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. MK-3475 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 MK-3475 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 NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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 patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Approximately 70-80% of patients with resectable metastatic disease will have disease recurrence following potentially curative treatment. The 1-year recurrence rate for this population is ~40-50% and another 15% of patients recur within the second year. In this study the primary endpoint is the 1-year recurrence rate. Secondary efficacy endpoints will include time to disease recurrence, median disease free survival and median overall survival.

4.2.3.2 Biomarker Research

4.2.3.2.1 Tumor lymphocyte infiltration

Multiple investigations have now demonstrated a correlation between the presence of tumor-infiltrating lymphocytes (TILs) in cancer tissue and a favorable prognosis. An increase in TILs is commonly being used as a surrogate marker for the development of an immune response in the setting of immune-based anti-cancer therapies. As part of this clinical trial, the presence of TILs will be determined in hepatic metastatic colorectal cancers following treatment with SBRT and pembrolizumab.

4.2.3.2.2 ^{18}F-FDG PET/MR

Traditionally, size has been used as the imaging biomarker where decreasing size indicates tumor response to therapy and increasing size denotes nonresponse. With newer cytostatic agents, size has been shown to be a poor indicator of tumor response. For example, hepatic metastases from gastrointestinal stromal tumors responding to imatinib therapy often initially increase in size. Clinical benefit despite progression per RECIST criteria has also been commonly observed with immunotherapies. Thus methods beyond RECIST criteria are needed for more accurately determining the response to immunotherapies. The novel imaging modality of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/ magnetic resonance imaging (PET/MR) allows evaluation of potential imaging biomarkers in addition to size to better evaluate disease response and predict overall clinical benefit.

Subjects may be determined to be ineligible for FDG PET/MR by a qualified physician. If subjects are ineligible, they will still be allowed to participate in the remainder of the study

procedures. If they are ineligible for FDG PET/MR, subjects may still undergo routine imaging with CT or MRI per standard of care, to be determined by their physician.

4.2.3.2.3 ^{18}F-FLT PET

3'-Deoxy-3'-[^{18}F]Fluorothymidine (FLT) PET/computed tomography (CT) uses a thymidine analogue that accumulates in proliferating tissue. Proliferating tissue could include malignant lesions or immune cells. In a study of patients with melanoma treated intranodally with a dendritic cell vaccine, FLT PET/CT could detect uptake in treated lymph nodes compared to control lymph nodes following vaccination, uptake that persisted for up to 3 weeks. Consequently, FLT PET/CT will be useful as a molecular imaging tool to detect immune activation after administration of pembrolizumab. In addition, FLT PET/CT has been shown to be an effective imaging biomarker of response for a variety of cancer therapies, including radiation therapy.

Subjects will have option to decline FLT PET/CT imaging.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients must have mismatch repair (MMR) proficient metastatic colorectal adenocarcinoma with liver-confined metastatic disease and the therapeutic goal to eradicate all known evidence of disease with one further operation. The diagnosis of liver metastatic colorectal adenocarcinoma must be histologically confirmed. Mismatch repair proficiency may be confirmed with microsatellite instability (MSI) testing or by immunohistochemistry for MMR proteins. In addition, subjects must be a candidate for SBRT to at least one intra-hepatic lesion. There is no limit to the size or number of lesions, assuming all disease can be adequately resected leaving the patient with no evidence of disease. There is no limitation to the number of prior chemotherapies, however all patients must have received at least one prior line of chemotherapy for CRC. Patients may have had resection of extra-hepatic metastatic disease previously if it has been greater than 12 months since that resection and no new extra-hepatic disease has been found.

5.1.2 Subject Inclusion Criteria

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

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

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

3. Have a diagnosis of histologically confirmed metastatic colorectal cancer to the liver (no other sites of metastatic disease).

    a. Histologic confirmation of a colorectal primary tumor is acceptable if accompanied by radiographic evidence of metastatic disease.

4. Tumor must be mismatch repair (MMR) proficient as determined by microsatellite instability or immunohistochemistry for MMR proteins.

    a. Microsatellite instability testing must be MSI-stable or MSI-low.

    b. Or IHC for MMR proteins must demonstrate intact MMR proteins.

5. Patient must be a candidate for SBRT to at least one intrahepatic lesion. There is no limit on the number of intrahepatic lesions the patient may have.

6. Patient must be a surgical candidate with therapeutic goal of eradicating all known disease with one additional surgery. Portal venous embolization is permitted to ensure resectability.

7. Prior resection of extra-hepatic metastatic disease allowed if completed more than 12 months previous to study enrollment and no new extra-hepatic disease has been found.

8. Have measurable disease based on RECIST 1.1.

9. Fresh or archived colorectal cancer tissue, preferably from a hepatic metastatic site. Archival tissue is acceptable for enrollment into this study. Subjects who have no archival tissue available do not need to undergo a new biopsy solely for the purpose of this study.

10. Subjects must have received at least one prior line of chemotherapy including an irinotecan or oxaliplatin-fluoropyrimidine-based systemic treatment for colorectal cancer.

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

12. Demonstrate adequate organ function as defined in Table 1. These labs should be repeated if not completed within 10 days of SBRT treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L 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** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 5 X ULN for subjects with liver metastases
Albumin	>2.5 g/dL

Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤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
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
[a]Creatinine clearance should be calculated per institutional standard.	

13. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 10 days of initiating SBRT. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

14. 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 (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

15. 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.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the initiation of SBRT.

2. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 (first day of SBRT treatment) or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

3. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks 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. Prior radiotherapy to the liver is not allowed.

    - 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.

4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the initiation of SBRT.

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

6. Hypersensitivity to pembrolizumab or any of its excipients.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously resected brain metastases may participate provided it has been at least 6 months and no CNS progression has been identified.

9. 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 for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. 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.

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

14. 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.

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

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

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative or quantitative] is detected).

18. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatments

Pembrolizumab

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Admin	Regimen	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle for a total of 9 cycles	Experimental

Radiation Therapy

1-3 liver metastases will be treated with SBRT per patient.

Dose Specifications: SBRT treatment will consist of 40-60 Gy delivered in five fractions prescribed to the planning target volume (PTV). Ninety percent of the prescribed dose must encompass 95% of the PTV. The maximum dose to 0.05cc of the PTV will be 140% of the prescribed dose. The minimum dose to 0.05cc will be 80% of the prescribed dose except to achieve normal tissue constraints. The PTV will be covered by 95% of the prescription dose. SBRT may use 3D, intensity modulation radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) for treatment delivery. Image guidance with MRI, megavoltage CT or cone beam CT scans would be required.

Technical Factors: Radiation may be delivered with LINAC based photon beams of 4 MV or higher for 3D or IMRT, or alternatively with Cobalt ^{60} of 1.25MV if utilizing IMRT. Particle therapy is not allowed.

Treatment Planning: Simulation positioning will be determined by the treating physician. Typically, the patient will be simulated supine with arms above the head if feasible. If treatment is planned without realtime image guidance, immobilization is required using a vacuum bag, chemical mold, thorax board or alternative immobilization device. If realtime image guidance is used then no immobilization is required, though is allowed. Respiratory motion management with respiratory gating with breath hold is preferred if using MRI guided radiation, though use of an internal target volume (ITV) without motion control is acceptable. Use of active breathing control (ABC), an abdominal compression device, or realtime ultrasound gating is recommended. If using realtime MRI guided radiation, a 3D MRI in the treatment position will be obtained as simulation. All patients will undergo a helical simulation CT scan with slice thickness 3mm or less and this should best match the treatment position. Either a 4D CT scan, 4D MRI, maximum inhale and exhale scans, or a cine MRI is required if an ITV is used for treatment planning. Gadoxetate contrast for MRI and iodine contrast for CT are recommended.

Target Delineation: Diagnostic MRI or CT scan will be registered to the simulation scan and used for gross target volume (GTV) definition. GTV will contoured by the treating physician and defined as the visible tumor. No clinical target volume (CTV) expansion will be used. Planning target volume will be GTV plus 1- 5mm radially and 1 to 8mm superiorly and inferiorly as determined by the treating physician.

Normal Tissue Constraints: The normal tissues will be defined as organs at risk of radiation in the tumor vicinity. This includes liver, small bowel, large bowel, stomach, right and left kidneys, spinal cord, gall bladder and skin.

Organ at Risk	Dose Constraints
Liver - GTV	NTCP < 5% ; or 700 cc <15Gy and mean <15Gy
Kidneys (combined)	V15 < 35%
Small bowel, stomach, gall bladder	Max 0.1cc < 35Gy
Large bowel	Max 0.5cc < 35Gy
Spinal cord	Max 0.1cc < 25Gy
Skin	Max 0.1cc < 40Gy

Operative Management

At the time of study enrollment patients must require only one further operation to clear all evidence of disease untreated by SBRT. Portal venous embolization is permitted prior to SBRT to enhance resectability. If the future remnant liver does not enlarge as anticipated the patient will be treated off study and replaced. This will be at the discretion of the medical and surgical teams. This operation must include a partial hepatectomy and may also include resection of the primary tumor concurrently.

5.2.1 Pembrolizumab Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 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 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3
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 Grade 3 or 4, or recurrent Grade 2	Withhold Permanently discontinue	• 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
Diarrhea / Colitis	Grade 2 or 3 Grade 4	Withhold Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without 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.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• 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 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer	• Ensure adequate evaluation to confirm

	Grade 3 or 4	Permanently discontinue	corticosteroids	etiology and/or exclude other causes
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. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

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).

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 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration/Procedures

5.2.2.1 Stereotactic Body Radiotherapy

SBRT will be initiated on Day 0. This should be initiated within 4 weeks of signing informed consent. An additional 2 weeks will be allowed if necessary due to SBRT treatment planning. A consult with the radiation oncologist should occur prior to determination of patient's study eligibility. A consult completed prior to signing of consent is acceptable. If SBRT is not able to be started within the additional 2 week period the study PI must be notified of the delay. Continued participation will be considered by the study PI if the subject has had no clinical decline and laboratory results meet the 10 day pre-SBRT requirement. Additional imaging to reassess disease state will be per study PI discretion.

5.2.2.2 Pembrolizumab

One infusion of pembrolizumab will be administered pre-operatively and 8 cycles (21 day cycles) will be administered post-operatively. The pre-operative infusion should occur at least 2 weeks following completion of SBRT, but may be given up to 4 weeks post SBRT completion. Pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis.

Cycle 2 of pembrolizumab (first cycle of adjuvant therapy) should be given at least 4-8 weeks following operative management, but may occur as late as 12 weeks following.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort 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.

5.2.2.3 Operative Management

Operative management to definitively manage all known sites of metastatic disease should occur at least 2 weeks post pembrolizumab treatment, but may occur up to 4 weeks post pembrolizumab treatment. A consult with surgeon should occur prior to determination of patient's study eligibility. A consult completed prior to signing of consent is acceptable.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Not applicable.

5.4 Stratification

Not applicable.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or

vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase 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
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- 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 to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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 describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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 and in greater detail in the ECI guidance document. 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 is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification and specific AE management guidance.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **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 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	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 hrs	**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.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically

sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences as described in Section 5.2.1.2
- If pembrolizumab is not administered within 4 weeks of completion of SBRT (cycle 1), within 12 weeks of operative management (cycle 2), or within 6 weeks of prior pembrolizumab during the adjuvant setting (cycle 3-9).
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Not applicable.

5.9 Subject Replacement Strategy

Patients not completing study procedures (SBRT, initial dose of Pembrolizumab, and surgical resection) to reach no evidence of disease (NED) status will be replaced.

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

Trial Period:	Screening Phase	SBRT	Neoadj Tx	Operative Management	Adjuvant Tx				Post-Treatment		
Treatment Cycle/Title:	Main Study Screening		1		2[d]	3-4	5	6-9	Safety Follow- up	Surveillance Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to 0	0+14[a]	14-28 days post SBRT[b]	14 -28 days post neoadj. Tx[c]	± 3	± 3	± 3	± 3	30 days (+/- 7 days) post last study drug	Every 12 weeks (+/- 14 days) post safety visit	Every 12 weeks (+/- 14 days) post Safety Visit
Administrative Procedures											
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X		X		X	X	X	X			
Trial Treatment Administration			X		X	X	X	X			
Post-study anticancer therapy status											X
Survival Status										X	X
Clinical Procedures/Assessments											
Review Adverse Events	X		X		X	X	X	X	X	X[m]	X[m]
Full Physical Examination	X		X		X						
Directed Physical Examination						X	X	X	X	X	
Vital Signs and Weight	X		X		X	X	X	X	X	X	
ECOG Performance Status	X		X		X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG[j]	X	X[j]	X								
PT/INR and aPTT	X	X[i]									
CBC with Differential	X	X[i]	X		X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X[i]	X		X	X	X	X	X	X	
Urinalysis	X										
Hepatitis B and C	X										

Trial Period:	**Screening Phase**	**SBRT**	**Neoadj Tx**	**Operative Management**	**Adjuvant Tx**				**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening		1		2[d]	3-4	5	6-9	Safety Follow- up	Surveillance Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to 0	0+14[a]	14-28 days post SBRT[b]	14 -28 days post neoadj. Tx[c]	± 3	± 3	± 3	± 3	30 days (+/- 7 days) post last study drug	Every 12 weeks (+/- 14 days) post Safety Visit	Every 12 weeks (+/- 14 days) post Safety Visit
T3, FT4 and TSH	X		X		X	X	X	X	X		
CEA	X		X		X	X	X	X		X	
Efficacy Measurements											
Tumor Imaging (CT or MRI)[l]	X						X		X[n]	X	
Tumor Biopsies/Archival Tissue Collection/Correlatives											
Archival or Newly Obtained Tissue[e] Collection		X									
Resection Specimen Collection[f]				X							
^{18}F-FDG PET/MRI[g]		X	X	X							
^{18}F-FLT PET[h]		X	X	X							
PBMC collection[k]		X	X		X		X				

a. SBRT to be initiated on Day 0, though an additional 14 days is allowed if necessary for SBRT treatment planning.
b. The first infusion of pembrolizumab is to be administered at least 14 days following the completion of SBRT, up to an additional 14 days is allowed.
c. Operative management will occur at least 14 days following the infusion of the first cycle of pembrolizumab, up to an additional 14 days is allowed.
d. Cycle 2 Day 1 must be completed within 12 weeks of operative management or patient will be removed from the study.
e. Archival or newly obtained FFPE tissue, if available, will be obtained at the time of study enrollment. If no tissue is available, subjects do not need to undergo a new biopsy solely for the purpose of this study.
f. The day of the patient's operation, fresh tissue will be collected by the UWCCC Biobank and aliquots will be frozen and/or fixed in formalin.
g. FDG PET/MRI will be obtained at baseline (pre-SBRT), prior to the first infusion of pembrolizumab, and again prior to each subject's operation.
h. (Optional) FLT PET will be obtained on a subset of subjects at similar time points, but not on the same days as the FDG PET imaging. Baseline FLT PET will be done pre-SBRT.
i. CBC, CMP PT/INR, aPTT to be repeated if screening labs not within 10 days of start of SBRT. The CMP to be completed is per UWHC standard (not per table 5).
j. Pregnancy test will be completed within 10 days of start of SBRT, and within 72 hours of first dose of pembrolizumab for women of child-bearing potential only.
k. PBMC collection: 5-10 mL heparinized green top tubes to be drawn at each timepoint (total of 50 mL). The SBRT sample may be drawn after eligibility is confirmed, but should be drawn prior to start of SBRT.
l. Tumor Imaging: Imaging of chest/abdomen and pelvis to be completed via CT or MRI. CTs of abdomen and pelvis to be completed with contrast; chest CT can be done with or without contrast. All protocol required imaging is to be completed using same modality as baseline scans. Baseline imaging completed within the screening period does not need to be repeated prior to start of SBRT unless the treating physician deems it clinically necessary. Imaging completed during study treatment has a +/- 7 day window for scheduling. Imaging completed per surveillance follow up has a +/- 14 day scheduling window.
m. Adverse event assessment as needed per section 7.1.5.3.1
n. If a subject stops treatment due to progressive disease (on imaging), repeat imaging is not required at the 30 day safety visit.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

Not applicable

7.1.1.7 Assignment of Randomization Number

Not applicable

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Not applicable

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening, after SBRT/prior to pembrolizumab, and after operative management prior to resuming pembrolizumab.

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

7.1.2.6.1 Standard of Care Assessment of Disease

For patients who have signs or symptoms in which imaging is clinically indicated, the decision of timing of radiographic studies remains at the discretion of the treating clinician. For asymptomatic surveillance after the completion of resection, CEA testing and scans will be completed every 3 months for 2 year. After 2 years scans will be completed every 6 months for 3 years and scans beyond 5 years from the metastatectomy will be at the discretion of the treating clinician. The first scan will occur prior to cycle 5 of pembrolizumab. Following the completion of pembrolizumab therapy, CEA and scans may be performed +/- 1 month of next testing due date. Either MRI or CT may be used for surveillance, however once a method is chosen that method should be used for the remainder of the surveillance protocol. The use of the FDA approved imaging agent, iohexol for CT scans would be within the approved indications.

At the time of each evaluation, patients will be classified in the following manner:

No evidence of disease (NED) or **Recurrence of disease (REC):** Recurrence must be confirmed by imaging and/or biopsy. Elevated CEA levels only or physical findings only will not be accepted as evidence of recurrence.

7.1.2.6.2 ^{18}F-Fluorodeoxyglucose (FDG) PET/MR Evaluation

A total of three scans will be performed per patient. These will be obtained prior to SBRT, prior to pembrolizumab and prior to operative management. Examinations will be performed in WIMR on an integrated PET/MR scanner, utilizing a 3T wide bore MR scanner (General Electric MR750w) with a lutetium-based scintillator PET insert with 24 detector rings. The PET/ MR hardware are FDA approved as are the MR sequences to be used, however UW investigators may also write some MR software in-house that would not be FDA-approved but would have non-significant risk status. Such software developed by UW researchers includes GE source code for the FDA-cleared device which is shared with UW under a research agreement. Included within the scope of the investigational software are added pulse sequencing and data processing capabilities in an attempt to:

- Improve image spatial resolution (create sharper images);
- Decrease acquisition time (or improve temporal resolution);
- Decrease image imperfections (e.g. noise, artifacts) that stem from system imperfections, finite acquisition time, signal variability, and physiological motion;
- Improve image contrast (draw out image features based on various material and functional properties);
- Improve quantitative measurements of the system or subject derived from the encoded signals; and
- Image non-proton nuclei (for cases where the FDA-cleared software does not function with non-proton coils).

Excluded from scope of the investigational software are any changes that would:

- Alter any safety-related specifications of the system – e.g., there can be no increase to RF power deposition, gradient switching rates, or acoustic noise beyond the IEC limits established for the baseline system.
- Impact the operation of the MRI scanner when the non-standard software is not engaged. Additionally, ^{18}FDG and gadoxetate disodium hold FDA approval for the indication for which they are being used in this study. The FDA has approved the use of gadolinium based contrast agents for use in magnetic resonance (MR) imaging.

Study Scan
Standard of care pre-exam screening including patient contraindications for MR, assessment of renal function, and possibility of pregnancy will be undertaken. Patients will be asked to fast for 6 hours (water is allowed) prior to the FDG PET/MR scan as per standard UW clinical care for FDG PET exams. If needed for diabetic patients, a clinical team consult will take place to discuss fasting safety, and a glucose measurement will be taken prior to the PET scan as per standard UW clinical care for PET exams. Patients who endorse claustrophobia may be prescribed a sedative by a qualified investigator to take prior to the scan per standard UW clinical care. Prior to the scan, a peripheral IV will be placed to allow injection of the PET tracer and MR gadolinium agent during the exams. For the MR portion, gadoxetate disodium (0.025 mmol/kg) will be administered intravenously to allow post contrast imaging. For the PET portion, 10 mCi +/- 10% (0.14 mCi/kg weight) of ^{18}fluorodeoxyglucose will be administered. The injection will occur prior to the MR imaging to allow biodistribution of this agent (approximately 60 minutes). All exams will be interpreted prospectively by a fellowship trained radiologist who is listed as key personnel on this study.

Standard of Care Scan
The MRI data gathered during the FDG PET/MRI scan may be used for routine clinical care if the following conditions are met:

- MR sequences to be used for clinical care that are run during the PET/MRI are consistent with sequences approved by the FDA for the condition under study
- The MRI is ordered by a qualified investigator, the images are read by a qualified UW Radiologist, and the MR images and report uploaded to the subject's medical record

7.1.2.6.3 FLT PET

To ensure uniformity as well as optimal data interpretation, analyses will be conducted under the supervision of Dr. Robert Jeraj, PhD (co-investigator) at the University of Wisconsin Image Analysis Core (IMAC) facility, with all radiographic analysis by Dr. Jeraj and designees.

- At the beginning of each imaging session, a CT scan will be obtained on the combined PET/CT scanner. The CT scan is an integral part of the PET/CT acquisition and serves for attenuation correction calculations and better PET/CT image co-registration. It will enable better delineation of the patient anatomy, which will be important when comparing different scans. An FLT-PET scan will follow. The patients will be injected up to 10 mCi (370MBq) +/- 10% of ^{18}F- FLT. The FLT tracer is not FDA approved. The FLT tracer will be used and cross-referenced under the currently active FDA Type II Drug Master File.

- Dynamic imaging over the liver region will be performed first to obtain arterial input function and post injection kinetics of the tracer. The field of view will be positioned so that either a tumor mass or axillary draining nodes will be in the field of view. The dynamic scan will be performed for 30 minutes. The arterial blood decay curve of ^{18}F-FLT will be estimated from the time-dependent activity in the left ventricular blood pool. The arterio-venous difference will be quantitatively assayed from the time-dependent activity in the right cardiac chambers.
- After the initial dynamic imaging a static whole body scan will be initiated. The whole body scan will be initiated at approximately 60 minutes after the injection. To minimize errors of the relative change assessment, the subsequent whole body scans will be initiated within 5 minutes of the initiation time of the baseline scan. The whole body scan will be performed with up to 10 minutes/scanning position, lasting up to 60 minutes. The patient will be scanned "head first". Together with the dynamic imaging, the total body scanning time will be up to 90 minutes (30 minutes dynamic plus up to 60 minutes static whole body scan).
- All the scans will be acquired in a 3D mode to increase spatial resolution of the imaging data.

FLT-PET/CT image reconstruction:

- For both the dynamic and whole body scans, two PET image reconstructions will be used – optimal qualitative and optimal quantitative reconstructions. The optimal quantitative reconstruction will be used for quantitative evaluation; the optimal qualitative reconstruction will be used for clinical read of the FLT PET/CT scans.

FLT-PET/CT image analysis:

- All the PET image data will be coregistered to the baseline (pretreatment) image data to enable comparison of the spatially dependent changes of the investigated tumor and lymph nodes and metastasis parameters during the therapy. The scans will be coregistered based on the CT data. Each of the lesions/lymph nodes will be coregistered locally, segmented and treated individually. Up to five metastases will be used in this analysis. Both the CT data, as well as the corresponding FLT PET data, will be analyzed for spatial correlation. The correlation coefficients, as well as joint histograms, will be used to evaluate similarity of the distributions.
- The CT data will be analyzed to establish anatomical changes in tumor size. Evaluation will be based on the change of the volume of the metastatic mass, as segmented from a CT scan: $\Delta V = V_{follow\text{-}up} - V_{baseline}$.
- The dynamic FLT-PET/CT imaging data will be used to perform kinetic analysis of the imaging data, thus allowing increase correlation to the biological parameters (cell proliferation index).
- The static total body FLT PET/CT imaging data will be used to identify tumor masses. Each of the metastasis will be treated individually. Standardized uptake values (SUV) will be used to assess the FLT PET uptake. SUVmax, SUVmean and SUVtotal will be recorded and analyzed. In addition, the spatial distribution of the change will be determined, in case of heterogeneous tumor uptake distribution.

7.1.2.7 Tumor Tissue Collection and Correlative Studies

7.1.2.7.1 PDL1 Immunohistochemistry

QualTek is a specialty CRO with a GLP and CAP/CLIA accredited laboratory which provides IHC services for biomarker driven clinical studies. QualTek developed and validated a PD-L1 IHC assay using Merck's proprietary 22C3 antibody. This assay has served as the prototype companion diagnostic assay and has been used by QualTek to test thousands of clinical samples, including those for prospective enrollment. A specimen from prior to study enrollment and up to three post treatment samples will be examined per patient.

This assay in not FDA approved, however, because it is does not cause any significant risk to subjects and is not being used for diagnostic purposes it would meet criteria for an exempt diagnostic device. For further details related to this assay please refer to the Laboratory Manual.

Immunohistochemistry Requirements

1. Samples may be held as blocks indefinitely at the site and shipped in batches.
2. As per Merck protocol requirements, FFPE blocks must be shipped cold (2-8°C) and in the dark using the shipping materials provided by QualTek. Be advised that blocks received that do not meet these conditions may affect PD-L1 staining.
3. Samples provided should contain tumor specimen sufficient for pathology review and analysis of tumor sample. If available, greater than 50% tumor content is preferred.
4. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, lavage specimen, frozen sample, plastic embedded sample, or formalin fixed sample that was frozen at any point **will not be accepted** for IHC analysis. Needle core biopsies that are formalin-fixed and paraffin-embedded are acceptable.

7.1.2.7.2 Tumor Infiltrating Lymphocytes

Immunohistochemical studies will be performed on formalin-fixed/paraffin-embedded tumor tissue. A total of 10 FFPE sections will be obtained from archived tissue obtained prior to initiating study treatment and from up to three liver lesions at the time of operative management following pembrolizumab treatment. IHC will be performed per standardized protocols for CD3, CD4, CD8, CD20 and CD45RO and potentially other biomarkers of response. Omission of the primary antibody will be used as a negative control along with positive control tissue. Semi-automated quantitative brightfield assessment of expression will be performed using the Vectra imaging system (PerkinElmer) and inForm analysis software system. A scanning protocol will be generated based on the tissue size and location of the cancer within the sample. Biomarker quantification will be calculated as a continuous variable (mean optical density) and also as quartiles (ex. 0, 1+, 2+, or 3+).

7.1.2.7.3 Banking of Tissue and PBMCs for Future Investigations

The University of Wisconsin Carbone Cancer Center Biobank will be notified of all subjects undergoing resection as part of this protocol. At the time of the operation, the tissue will be transferred to surgical pathology and residual tissue will be collected by the Biobank staff. Tissue will be then be transferred to Deming Laboratory staff for storage and future studies including but not limited to tissue culture, RNA, DNA and protein analyses. In addition, PBMCs

will be collected as per the study calendar and transferred to the Deming Laboratory, coded, and labeled with the study ID number and date of collection for storage and analysis. Residual blood specimens remaining after collection of PBMCs will be banked for future studies including but not limited to RNA, DNA, ctDNA and protein analyses for research purposes only. This includes sending samples to commercial vendors such as Personal Genome Diagnostics, Foundation Medicine, Tempus or Gardant Health.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Free thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

After Cycle 1 (pembrolizumab), pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing of subsequent cycles of pembrolizumab. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

Not applicable.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

Not applicable.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

7.1.5.1.1 Screening Period

The screening period begins with the signing of informed consent. This period is 28 days in length or the time to the initiation of SBRT. An additional 14 days is allowed for the initiation of SBRT if all other study screening procedures are completed to allow for scheduling and planning of SBRT. If a subject signs consent, and does not start study screening activities (labs, imaging requirements) for reasons such as insurance concerns or vacation,they may sign a new consent form to re-start the screening period. All screening and eligibility requirements need to be met based on the date of the newly signed consent form. Subjects who have completed screening activities, but do not meet eligibility criteria within the original screening period, may not re-sign the consent form and are considered ineligible for the study.

7.1.5.2 Treatment Period

The treatment period is defined as the time from initiation of SBRT through the completion of the final cycle of pembrolizumab.

7.1.5.3 Post-Treatment Visits

Post-treatment visits will begin following the completion of the final cycle of pembrolizumab and will be completed according to the study calendar in section 6.0.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE (considered to be possibly, probably or definitely related to protocol therapy) of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.4 Surveillance Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Surveillance Follow-Up Phase and should be assessed every 12 weeks (± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 14 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone, or in person, every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first Adverse events (considered to be possibly, probably or definitely related to protocol therapy) recorded at the time of the Safety Follow-Up visit should continue to be followed until resolution of the AE to Grade 0-1 or until the treating physician considers the AE to be permanent.

7.1.5.5 Second Course Phase (Retreatment Period)

Not applicable.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency

and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

Expected Adverse Events resulting from the surgical intervention will not be reported unless that adverse event is possibly, probably or definitely attributed to the investigational drug. Unexpected adverse events resulting from surgical intervention will be reported regardless of attribution.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

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 associated with ("results from") 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."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 6 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

7.3 UWCCC Review and Oversight Requirements

a) Serious Adverse Event – Reported Within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database. The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC. If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

b) Serious Adverse Event – Reported within 10 Days

Serious Adverse Events requiring reporting within 10 days must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database. The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these

notifications to the DSMC. If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

c) Sponsor-Investigator Responsibilities for SAE Review

In the event the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1) **suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) **unexpectedness** (the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed) in the context of this study. SAE with suspected causality to study drug and deemed unexpected are reported as IND Safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 15 calendar days. All fatal or life-threatening SAE that are unexpected and have suspected causality to the study drug will be reported by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 7 calendar days.

Refer to Section II.E for UWCCC PI instructions for reporting to the FDA.

d) Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

7.4 EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table *[6]* below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to sections A and B below if the SAE occurred at the UWCCC or sections C and D if the SAE occurred at 1 South Park, Johnson Creek, or a WON Site.

TABLE 6. **Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1,2]**

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)

NOTE: Investigators **MUST** immediately report to the *UWCCC* and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An adverse event is considered serious if it results in ANY of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria* **MUST** be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in hospitalization ≥ 24 hrs	10 Calendar Days	24 Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited reporting exceptions: Please refer to section 7.2 for exceptions related to surgical intervention.

Expedited AE reporting timelines are defined as:

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

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

SAE Requiring *[24]* Hour Reporting Occurs at UWCCC:

1. Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[24]* hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial *[24]* hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Dustin Deming - ddeming@medicine.wisc.edu
c) Renae Quale: rmq@medicine.wisc.edu
d) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

2. Report to the Sponsor:

See sponsor reporting information above.

3. Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

SAE Requiring *[10]* Day Reporting Occurs at UWCCC:

1. Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[10]* day reports.

For this protocol, the following entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Any appropriate parties listed on SAE Routing Form

2. Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

3. Report to the Sponsor:

See separate reporting information above.

Other Reporting Requirements

Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

7.4.1 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. Additional adverse events:

   Events thought to be immune-mediated (both non-serious and serious adverse events) from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

   Subjects should be assessed for possible immune-mediated events prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an event thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related event, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.4.2 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:**V4.0**	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.4.3 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Endpoints

8.1.1 Safety and Tolerability: Adverse Events and Toxicities

Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

8.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint will be the recurrence rate at 1 year following clearance of metastatic disease in the setting of treatment with SBRT and pembrolizumab.

8.1.3 Secondary Efficacy Endpoints

Secondary endpoints will include time to recurrence, disease-free survival and overall survival. Time to recurrence will be defined from the date of enrollment to the date of documented disease recurrence, overall survival will be defined from the date of enrollment to date of death (any cause) or last date of follow-up.

8.1.4 Exploratory Endpoints

Exploratory endpoints will include PET/MR imaging parameters, tumor-infiltrating lymphocytes and expression levels of PDL1.

8.2 Sample Size and Power Calculation

The primary objectives are (1) to determine the safety and tolerability of pembrolizumab in combination with SBRT to the liver, and (2) to determine the recurrence rate at 1 year following clearance of metastatic disease in the setting of treatment with SBRT and pembrolizumab. A total sample size of 15 patients is proposed for this trial. The proposed sample size of 15 patients is adequate to provide sufficient accuracy in estimating toxicity rates. Specifically, with a sample size of 15, toxicity rates will be estimated with a standard error of less than 15% and the 95% confidence intervals will be no wider than 45%.

The following table shows the probabilities for observing at least K (K=1, 2, 3) toxicity events in 15 patients for toxicity rates ranging between 5-35%.

Table 8: Probability for observing at least K (K=1, 2, 3) toxicity events in 15 patients for toxicity rates ranging between 5-35%

	Toxicity Rate						
K	5%	10%	15%	20%	25%	30%	35%
1	0.54	0.80	0.91	0.96	0.99	>0.99	>0.99
2	0.17	0.45	0.68	0.83	0.92	0.96	0.99
3	0.04	0.18	0.40	0.60	0.76	0.87	0.94

Hence, if the true toxicity rate is at least 10%, there is a high likelihood that at a toxicity event will be observed in at least one out of 15 patients. Specifically, the probability of observing a severe toxicity in at least one of 15 patients is 80% if the true toxicity rate is 10%. Analogously, if the true toxicity rate is 20%, there is a 96% chance of observing at least one toxicity event in 15 patients.

Furthermore, the proposed sample size of 15 is also sufficient for a preliminary efficacy evaluation. The primary endpoint for the preliminary efficacy evaluation will be the recurrence rate at 1 year following clearance of metastatic disease in the setting of treatment with SBRT and pembrolizumab. If the recurrence rate at year 1 following clearance of metastatic disease is 60% or more, the efficacy of the proposed SBRT and pembrolizumab treatment combination will be considered as unacceptably low. Hence, the null hypothesis that the recurrence rate at year 1 is at least 60% will be tested against the alternative hypothesis that the recurrence rate is less than 60%. It is anticipated that the proposed SBRT and pembrolizumab treatment will substantially reduce (>50%) the recurrence rate at year 1. An anticipated reduction of the recurrence at year 1 form 60 to 30% will be detected with 85% power at the one-sided 0.10 significance level with the proposed sample size of 15.

8.3 Statistical Analysis Plan

8.3.1 General

The statistical analysis will be reported using summary tables, figures, and data listings. Continuous variables will be summarized by standard descriptive statistics in terms of means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the case report forms as well as any derived data will be included in data listings. Data analysis will be performed using SAS® version 9.4 or greater.

A formal statistical analysis plan (SAP) will be developed before the database lock. It will include detailed descriptions of summaries and mock-ups of tables, listings, and figures to be included in the clinical study report.

8.3.2 Demographics

Demographic variables and baseline characteristics measured on a continuous scale will be summarized in terms of number of subjects, means, standard deviations, medians and ranges, stratified by study arm. Categorical demographic variables and baseline characteristics will be summarized in tabular format.

8.3.3 Safety Analysis

Adverse events and toxicity will be categorized by type, severity and attribution, and will be summarized in tabular format. The proportions of patients with grade ≥1, grade ≥ 2, and grade ≥ 3 toxicities will be reported along with the corresponding 95% confidence intervals. The 95% confidence intervals of the toxicity rates will be constructed using the Wilson score method.

8.3.4 Primary Efficacy Analysis

The number and frequencies of recurrences will be summarized in tabular format. The null hypothesis that the recurrence rate at year 1 is at least 60% will be tested against the alternative hypothesis that the recurrence rate at year 1 is less than 60%. The 95% confidence intervals of the recurrence rate at year 1 will be constructed using the Wilson score method

8.3.5 Secondary Efficacy Analysis

Time to recurrence, disease free survival and overall survival will be estimated using the Kaplan-Meier method. The 95% confidence of the median time to recurrence, disease free survival and overall survival will be calculated using the Brookmeyer-Crowley method.

8.3.6 Exploratory Endpoints Analysis

Imaging biomarkers (SUVtot, SUVmean, SUVmax) will be summarized using standard descriptive statistics in terms of means, standard deviations, medians, and ranges. Percentage changes in imaging biomarkers will be calculated between assessment time points. Logistic regression analysis will be conducted to evaluate whether changes in imaging biomarkers predict the recurrence rate at 1 year following clearance of metastatic disease.

The number of tumor-infiltrating lymphocytes will be summarized in terms of means and standard deviations for each assessment time point. A negative binomial regression or overdispersed Poisson regression model with patient specific random effects will be used to evaluate changes in the number of tumor-infiltrating lymphocytes.

Linear regression analysis will be conducted to examine the correlation between expression levels of PDL1 in CRC liver metastases.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by the FDA and/or other applicable regulatory authority. The access may consist of study-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections. Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

10.2 Compliance with Law, Audit and Debarment

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements. This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Merck with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.
The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee re-approval throughout the duration of the study. The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected. The Investigator is also required to notify the FDA in writing of any SAE that is both unexpected and related to the study drug, within 15 days of knowledge of the event, and within 7 days of a death related to the study drug.

10.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.4 Quality Management System

Protocols subject to intensive monitoring generally include UW Institutional Phase I and Institutional Trials of any phase involving recombinant DNA/gene transfer. These protocols undergo continuous review of data and subject safety at weekly Phase I/Disease Oriented Team (DOT) meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOWG meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a quarterly basis by the study team for review by the UWCCC Data and Safety Monitoring Committee (DSMC).

10.5 Data Management

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification is of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.