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Document:

Study Protocol and Statistical Analysis Plan

Official Study Title:

A Multi-Centre, Single Arm, Phase 2 Trial of Pembrolizumab in Treatment Naïve Patients with Poor-Prognosis Carcinoma of Unknown Primary Site

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SIGNATURE PAGE

By signing below, the qualified Investigator, at the site, agrees to adhere to the protocol. All Health Canada approved protocol amendments must receive local Research Ethics Board (REB) approval prior to implementation.

The Qualified Investigator also agree(s) to conduct the study in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines (ICH GCP).

The Qualified Investigator at the site also thereby agrees the REB will approve all patient informed consent forms before being presented to the patient. The Investigator will obtain informed consent and document this process for all patients enrolled on this study.

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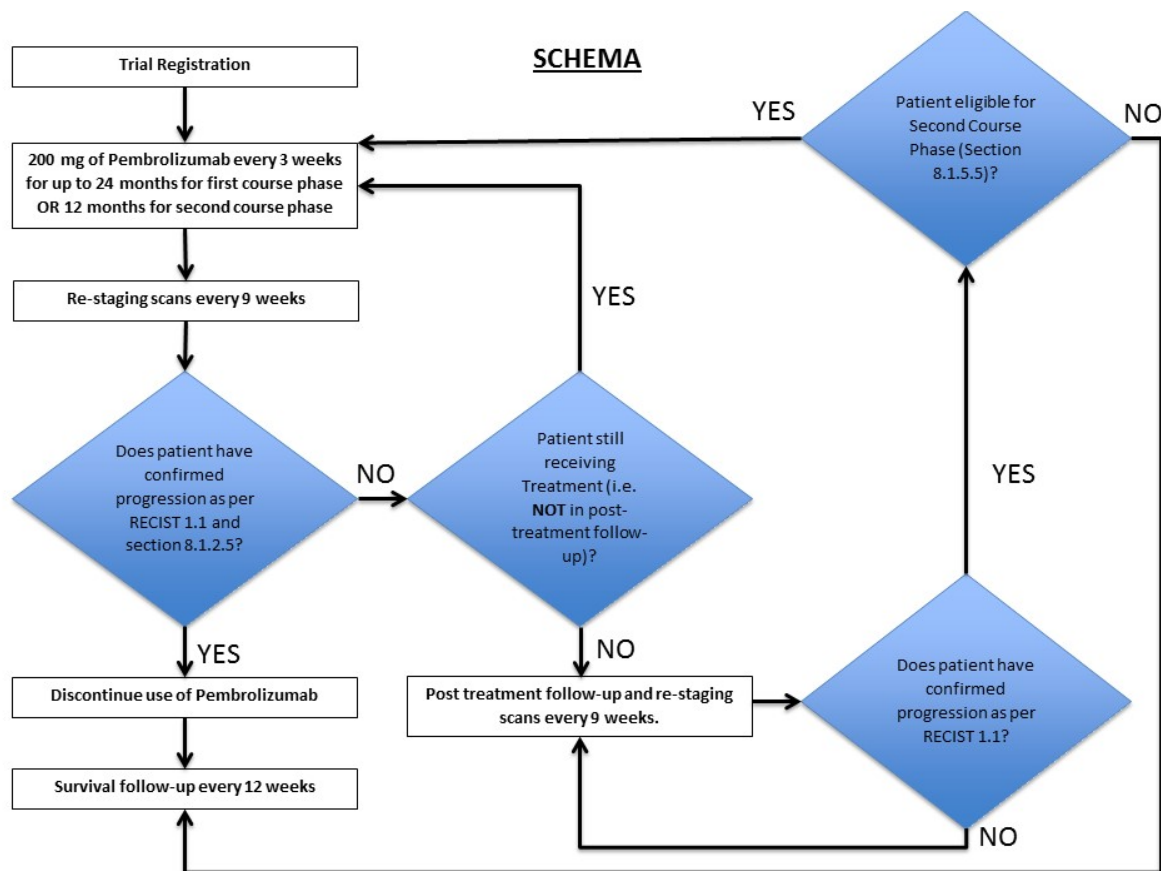


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1.0 LIST OF ABBREVIATIONS

aPTT	Activated Partial Thromboplastin Time
ADL	Activities of Daily Living
AE	Adverse Event/Adverse Experience
AFP	Alpha-fetoprotein
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline phosphatase
β-hCG	β-Human Chorionic Gonadotropin
BCG	Bacillus Calmette-Guerin
BRAF	B-Raf Proto-Oncogene, serine/Threonine kinase
CD3	Cluster of Differentiation 3
CD28	Cluster of Differentiation 28
CD4+	Cluster of Differentiation 4
CD8+	Cluster of Differentiation 8
CNS	Central Nervous System
CrCl	Creatinine Clearance
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein-4
CUP	Carcinoma of Unknown Primary Site
ECI(s)	Event(s) of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
EPO	Erythropoietin
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FT4	Free thyroxine
FOXP3	Forkhead Box P3
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCV RNA	Hepatitis C Virus Ribonucleic Acid
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IgG4/kappa	Immunoglobulin 4

IgV	Immunoglobulin Variable Region
IgC	Immunoglobulin Constant Region
IL-2	Interleukin 2
INR	International Normalized Ratio
ITIM	Immunoreceptor Tyrosine Based Inhibition Motif
ITSM	Immunoreceptor Tyrosine Based Switch Motif
IV	Intravenous
LDH	Lactate Dehydrogenase
Magnetic Resonance Imaging	MRI
mAb	Monoclonal Antibody
NCI	National Cancer Institute
NLR	Neutrophil/Lymphocyte Ratio
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Lung Cell Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over the Counter
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Receptor-Ligand 1
PD-L2	Programmed Death Receptor-Ligand 2
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PKC	Protein Kinase C
PM	Product Monograph
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Prothrombin Time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
REB	Research Ethics Board
RECIST®	Response Evaluation Criteria in Solid Tumors
SHP-1	Src Homology Region 2 Domain Containing Phosphatase-1
SHP-2	Src Homology Region 2 Domain Containing Phosphatase-2
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Stable Disease
SGOT (same as AST)	Serum Glutamic Oxaloacetic Transaminase
SGPT (same as ALT)	Serum Glutamic Pyruvic Transaminase
SJS	Stevens-Johnson syndrome

SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
T3	Total Triiodothyronine
T4	Free thyroxine
TB	Tuberculosis Bacillus
TEN	Toxic epidermal necrolysis
TILs	Tumor Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
ZAP70	Zeta-Chain-Associated Protein Kinase 70

2.0 TRIAL SUMMARY

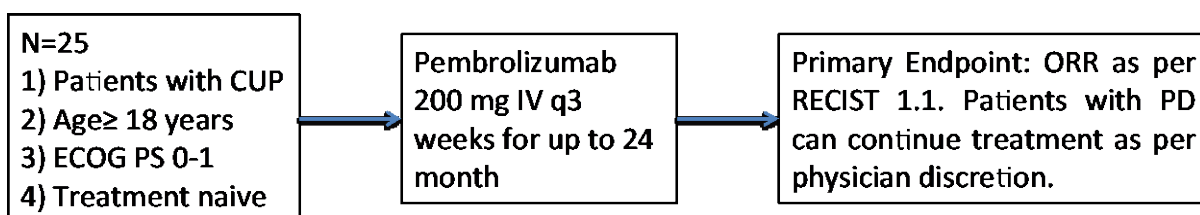
Abbreviated Title	Pembrolizumab in Patients with Poor-Prognosis Carcinoma of Unknown Primary Site (CUP)
Trial Phase	2
Clinical Indication	Treatment naïve patients with poor prognosis carcinoma of unknown primary site
Trial Type	Single arm phase 2
Type of control	Not applicable
Route of administration	Intravenous
Trial Blinding	Not applicable
Treatment Group	Pembrolizumab 200 mg IV every 3 weeks for up to 24 months.
Total Number of trial subjects	25
Estimated enrollment period	24 months
Estimated duration of trial	48 months
Duration of Participation	24 months

3.0 TRIAL DESIGN

3.1 Trial Design

This is a multi-centre, single arm phase 2 study of Pembrolizumab (Keytruda™ or MK-3475) in treatment naïve patients with poor prognosis carcinoma of unknown primary site (CUP). Participants will receive Pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle for up to 24 months. Patients will be evaluated for response every 9 weeks. Patients with objective response to treatment and those with stable disease will continue to receive Pembrolizumab. Patients with tumor progression will be discontinued from the study. Patients with progressive disease (PD), but showing a clinical benefit, may continue on Pembrolizumab, as per the discretion of the responsible Qualified Investigator. Response will be evaluated as per Response Evaluation Criteria in Solid Tumors (RECIST®) version 1.1 (see Section 12.3).

3.2 Trial Diagram



4.0 OBJECTIVES & HYPOTHESIS

4.1 Primary Objective(s) & Hypothesis

- (1) **Primary Objective:** To determine the safety and objective response rate (ORR) associated with Pembrolizumab in treatment-naïve patients with poor prognosis CUP.
- (2) **Secondary Objective(s):** To determine the overall survival (OS), progression free survival (PFS), and duration of response (DOR) associated with Pembrolizumab in patients with treatment-naïve poor prognosis CUP.
- (3) **Hypothesis:** Pembrolizumab will be tolerable and improve ORR in treatment-naïve patients with poor prognosis CUP.

4.2 Exploratory Objective

- (1) **Objective:** To evaluate the prognosis and predictive value of the neutrophil/lymphocyte ratio (NLR) with Pembrolizumab treatment. Also, the predictive value of programmed death receptor-1 ligand (PD-L1) tumor expression with Pembrolizumab treatment will be evaluated.

5.0 BACKGROUND & TRIAL RATIONALE

5.1 Background

Refer to the Product Monograph (PM) for detailed background information on Pembrolizumab.

5.1.1 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 cluster of differentiation 8 (CD8+) T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells is thought to correlate with improved prognosis and long-term survival in many solid tumors.

The programmed cell death protein 1 (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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte associated protein-4 (CTLA-4) which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed death receptor-ligand 2 (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, Src homology region 2 domain containing phosphatase-1 (SHP-1) and Src homology region 2 domain containing phosphatase-2 (SHP-2) to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as cluster of differentiation 3 zeta (CD3 ζ), protein kinase C-theta (PKC θ) and zeta-chain-associated protein kinase 70 (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 expressed on activated lymphocytes including peripheral cluster of differentiation 4 (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. 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. Pembrolizumab has recently been approved in the United States and Canada for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if B-raf proto-oncogene, serine/threonine kinase (BRAF) V600 mutation positive, a BRAF inhibitor.

5.1.2 Preclinical and Clinical Trial Data

Refer to the PM for Preclinical and Clinical data.

5.2 Trial Rationale

5.2.1 Rationale for the Trial and Selected Subject Population

CUP represents a heterogeneous group of cancers that present with metastatic epithelial disease with no identifiable primary lesion at the time of diagnosis [1]. CUP is a common clinical entity, accounting for 3-5% of all cancer diagnoses [1, 2]. Although several subsets with favourable prognoses have been identified based on clinicopathological features (such as gender, sites of disease involvement and histopathology), over 80% of patients do not fit into these subsets [1, 2]. In a systematic review of more than 700 patients with poor-prognosis CUP and liver metastases, histologically diagnosed as adenocarcinoma or undifferentiated carcinoma, response rates were less than 20% and median survival was 6–7 months [3]. A meta-analysis has shown that no type of chemotherapy has been proven to lengthen survival in this poor prognosis group and therefore, no standard first-line chemotherapy regimen has been established [4, 5].

CUP primary tumors are either too small to be found or have regressed entirely. Researchers hypothesize that these primary lesions are occult, dormant, indolent, or regressed, in part, due to anti-cancer immune surveillance [6]. In fact, lymphopenia is related to a poorer prognosis in patients with CUP, suggesting that impairment of lymphocytes may be associated with disease pathogenesis and the development of metastatic disease [7, 8]. Moreover, in 70 recently analyzed CUP cases, PD-1 expression in tumor-infiltrating lymphocytes and PD-L1 expression on cancer cells were observed in 63% and 21% of the cases, respectively. Co-expression of both markers was detected in 11 out of 70 (16%) tested cases [9]. Another study had a similar frequency of PD-L1 expression of 28% (8 of 29) in CUP cases [10]. No immunotherapy has ever been tested in this clinical setting and we hypothesize that Pembrolizumab will be tolerable to patients and show a positive clinical benefit in this patient population.

Testing the activity of Pembrolizumab in patients with CUP may also shed clues to the first-line activity of this agent in other cancer types. In an analysis of 12 post-mortem CUP cohort studies from 1944 to 2000, the primary tumor was identified in 644 (73%) of 884 patients. The most common primaries were lung (27%) and pancreatic tumors (24%); tumors in the liver or bile duct (8%), kidney or adrenals (8%), colon or rectum (7%), genital system (7%), and stomach (6%) were also reported [11]. Pembrolizumab has been tested and demonstrated activity in some of these cancers. Depending on the types of CUP patients recruited in this proposed study, it could shed light on other cancers where Pembrolizumab has first-line activity.

5.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Keynote-001) was conducted to evaluate the safety and clinical activity of single agent Pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) 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 Pembrolizumab displayed evidence of target engagement and reduction of tumor size at all dose levels (1 mg/kg, 3 mg/kg

and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date. The dose of 10.0 mg/kg Q2W was the highest dose tested in (Keynote-001) however recent data from other clinical studies within the Pembrolizumab program has shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

Pharmacokinetic (PK) data analysis of Pembrolizumab administered Q2W and every 3 weeks (Q3W) indicated slow systemic clearance, limited volume of distribution, and a long half-life (refer to PM). Pharmacodynamics data (interleukin 2 (IL-2) release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamics data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population PK analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of Pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for Pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the non-small lung cell cancer (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 Q3W will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose Q3W, 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.

5.2.3 Rationale for Endpoints

5.2.3.1 Efficacy Endpoints

In a systematic review of more than 700 patients with poor-prognosis CUP and liver metastases histologically diagnosed as adenocarcinoma or undifferentiated carcinoma, response rates were less than 20% and median survival was 6–7 months [3]. Another retrospective study of 118 CUP patients with liver metastases revealed overall response rates of 19.4% with administration of platinum combinations and 20% with non-platinum regimens [12]. As such, the null hypothesis that the true ORR is 20% will be tested against a one-sided alternative. In the first stage, 12 patients will be accrued. If there are 2 or fewer responses in these 12 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 25. The null hypothesis will be rejected if 8 or more responses are observed in 25 patients. This design yields a type I error rate of 0.1 and power of 0.8 when the true response rate is 40%. Moreover, higher response rate (greater than or equal to 30%) has been associated with statistically longer PFS and OS in this clinical setting [13].

5.2.3.2 Biomarker Research Rationale

Neutrophil/Lymphocyte Ratio (NLR): Inflammation is a prognostic marker in patients with CUP and the NLR, a measurement of inflammation is an externally validated prognostic marker in patients with CUP [14]. As these blood tests are part of routine managements, this biomarker research will not add cost to the trial. We hypothesize that the NLR will not only be prognostic in patients with CUP, but may also predict for response or stability of disease to Pembrolizumab treatment. NLR will be measured at baseline and at 4 months. The NLR will be calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The $NLR \geq 5$ will be considered elevated as previously described [15].

PD-L1 Expression of CUP Tumor: PD-L1 status will be assessed in archival or newly obtained tumor samples by means of immuno- histochemical analysis with the use of the PD-L1 specific antibody at the Qualtek Molecular Laboratories (6483 Calle Real, Suite A, Goleta, CA 93117, **Phone:** 805.681.3200, **Fax:** 805.830.6379, **Email:** samples@qmlabs.com).

6.0 METHODOLOGY

6.1 Subject Inclusion Criteria

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

1. Have histologically (or cytologically) documented, metastatic carcinoma with no primary site identified. The following tests are required to exclude a primary site of disease: complete history and physical examination, blood chemistry (including serum tumor marker for prostate-specific antigen (PSA) in men, alpha-fetoprotein (AFP), β -human chorionic gonadotropin (β -hCG)) and mammography in women, urinalysis, thoracic and abdominopelvic computed tomography scans, bone scan, and symptom or sign-oriented imaging or endoscopic studies).
2. Have adenocarcinoma, a poorly differentiated carcinoma, or any squamous cell carcinomas.
3. Be willing and able to provide written informed consent for this trial.
4. Be ≥ 18 years of age on day of signing informed consent.
5. Have documented measurable disease based on RECIST[®] 1.1. via Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI).
6. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 calendar days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived Formalin-Fixed, Paraffin-Embedded (FFPE) Block(s).*
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Must have a documented negative urine or serum pregnancy test within 7 days prior to receiving the first dose of study medication if female and of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.
9. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity from the time they sign the informed consent form prior to start of therapy through 120 calendar days after the last dose of study medication (reference Section 6.6.2). Subjects of childbearing potential are defined as those who have not been surgically sterilized or have not been free from menses for > 1 year.
10. Male subjects must agree to use 2 adequate methods of contraception from the time they sign the informed consent form prior to start of therapy through 120 calendar days after the last dose of study therapy. Examples include: condoms, spermicidal jelly, and abstinence.

11. Demonstrate adequate organ function as defined in Table 1 below. All screening labs must be performed within 7 calendar days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	$\geq 1.5 \times 10^9/\text{L}$
Platelets	$\geq 100 \times 10^9/\text{L}$
Hemoglobin	$\geq 90 \text{ g/L}$ or $\geq 5.6 \text{ mmol/L}$ without transfusion or erythropoietin (EPO) dependency (within 7 days of assessment)
Renal	
Serum creatinine	$\leq 1.5 \times$ upper limit of normal (ULN)
Calculated creatinine clearance ^a	$\geq 60 \text{ mL/min}$ for subject with serum creatinine levels $> 1.5 \times$ ULN
Hepatic	
Serum total bilirubin	$\leq 1.5 \times$ ULN OR Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5 \times$ ULN
AST (SGOT) ^b and ALT (SGPT) ^c	$\leq 2.5 \times$ ULN OR $\leq 5 \times$ ULN for subjects with liver metastases
Albumin	$\geq 25 \text{ mg/L}$
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5 \times$ ULN unless subject is receiving anticoagulant therapy as long as INR/PT or aPTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	$\leq 1.5 \times$ ULN unless subject is receiving anticoagulant therapy as long as INR/PT or aPTT is within therapeutic range of intended use of anticoagulants
^a Creatinine clearance must be calculated using the Cockcroft and Gault Formula (refer to Appendix - Section 12.4).	
^b Aspartate aminotransferase (AST) is the same as serum glutamic oxaloacetic transaminase (SGOT).	
^c Alanine aminotransferase (ALT) is the same as serum glutamic pyruvic transaminase (SGPT).	

6.2 Subject Exclusion Criteria

The subject is excluded from participating in this trial if the subject meets any of the following criteria:

1. CUP suspected to be lymphomas (e.g. staining for leukocyte common antigen), malignant melanoma (e.g. staining for both S100 and HMB45), extragonadal germ cell neoplasms (e.g. staining for both AFP and β -hCG), sarcomas (e.g. staining for cytokeratins and vimentin), neuroendocrine tumors (e.g. staining for chromogranin and synaptophysin), and prostatic adenocarcinomas in men (e.g. staining for PSA).

2. Patient subgroups that are suitable for well-defined treatments: (e.g. women with adenocarcinoma involving axillary lymph nodes as the only site of disease, women with papillary serous carcinoma of the peritoneum, patients with squamous cell carcinoma that involved either cervical or inguinal lymph nodes only, patients with poorly differentiated carcinomas that suggested germinal tumors and with elevated levels of β -hCG and/or AFP, and patients with carcinoma that involved a single, potentially resectable site) also are excluded from enrollment.
3. 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 first dose of treatment.
4. Has a confirmed diagnosis of immunodeficiency or is receiving documented systemic steroid therapy or any other form of immunosuppressive therapy within 7 calendar days prior to the first dose of Pembrolizumab.
5. Has a known history of active Tuberculosis Bacillus (TB).
6. Hypersensitivity to Pembrolizumab or any of its excipients (L-histidine, L-histidine hydrochloride monohydrate, Sucrose or Polysorbate 80).
7. Has had radiation therapy within 14 calendar days prior to the first dose of treatment. If subject undergone radiation, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy as per the discretion of the Qualified Investigator.
8. Has had prior chemotherapy, targeted small molecule therapy, or prior anti-cancer mAb.
9. If subject has undergone major surgery, they must have recovered adequately from the complications from the surgery prior to starting therapy as per the discretion of the Qualified Investigator.
10. 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.
11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by CT brain or MRI brain for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 calendar days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

12. 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.
13. Has a history of (non-infectious) pneumonitis or current pneumonitis.
14. Has an active infection requiring systemic therapy.
15. 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 Qualified Investigator.
16. Has known psychiatric or substance abuse disorders that would interfere with compliance with the requirements of the trial.
17. Is pregnant or breastfeeding, or planning to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 calendar days after the last dose of trial treatment.
18. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
19. Has a known history of Human Immunodeficiency Virus (HIV).
20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA is detected).
21. Has received a live vaccine within 30 calendar days of planned start of study therapy.
22. Has previous organ and/or bone marrow transplant.

6.3 Trial Treatments

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

Table 2 Trial Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment must begin within 3 calendar days of registration.

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

6.3.1 Dose Selection/Modification

6.3.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 5.0 – Background and Trial Rationale.

Details on preparation and administration of Pembrolizumab are provided in the Study Pharmacy Manual.

6.3.1.2 Dose Modification

Both serious and non-serious adverse events (AEs) associated with Pembrolizumab are likely immune related in nature. These AEs 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. For information regarding the use of corticosteroids and supportive care guidelines, **refer to Section 6.5.1.**

All grading is done according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) Version 4.0 for AEs and events of clinical interest (ECIs) (see Section 12.2).

Table 3: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For CTCAE Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1 and corticosteroid has been tapered	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Increased AST, ALT, or Bilirubin	2	Toxicity resolves to Grade 0-1 and corticosteroid has been tapered (see exception below) ¹	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold Pembrolizumab for new onset T1DM or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume Pembrolizumab when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).
Hypophysitis	2	Withhold Pembrolizumab until toxicity resolves to Grade 0-1 and corticosteroid has been tapered.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Withhold <u>or</u> permanently discontinue ² If held, resume Pembrolizumab when AE resolves to ≤ Grade 2, is controlled with hormonal replacement therapy, and after corticosteroid taper, if needed	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks <u>or</u> permanently discontinue ² .

Toxicity	Hold Treatment For CTCAE Grade	Timing for Restarting Treatment	Discontinue Subject
Hyperthyroidism	2	Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted.	Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Hyperthyroidism	3-4	Withhold <u>or</u> permanently discontinue ² If held, resume Pembrolizumab when AE resolves to $\leq$ Grade 2 and is controlled with hormonal replacement therapy	Toxicity does not resolve within 12 weeks of last dose <u>or</u> permanently discontinue ² .
Hypothyroidism	2-4	Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted.	Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1 and corticosteroid has been tapered	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4, or recurrent Grade 2	Permanently discontinue	Permanently discontinue
Renal Dysfunction or Nephritis	2	Toxicity resolves to Grade 0-1 and corticosteroid has been tapered	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Myocarditis	1-2	Toxicity resolves to Grade 0-1 and corticosteroid has been tapered	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Skin Reactions (includes Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN))	3 or <u>suspected</u> SJS or TEN	Toxicity resolves to Grade 0-1 and corticosteroid has been tapered	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4 or <u>confirmed</u> SJS or TEN	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	Intolerable/persistent Grade 2	Toxicity resolves to Grade 0-1 and corticosteroid has been tapered	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3	Hold until toxicity resolves to Grade 0-1 and corticosteroid has been tapered <u>Or</u> permanently discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks <u>or</u> permanently discontinue.
	4 or recurrent Grade 3	Permanently discontinue	Permanently discontinue
Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs. Also permanently discontinue for any life-threatening event (excluding endocrinopathies controlled with hormone replacement therapy). ¹ For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued. ² Withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator or treating physician.			

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 re-started on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. All reasons for study treatment interruption must be documented in the patient's study record and in the patient's case report form (CRF).

6.3.2 Timing of Dose Administration

Trial treatment is to be administered on Day 1 of each cycle +/- 3 calendar days after all procedures/assessments have been completed as detailed on the Trial Flow Charts (Section 7.0). Pembrolizumab 200 mg will be administered as a 30 minute IV infusion Q3W. The sites should make every effort to target infusion timing to be close to 30 mins 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).

6.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Prohibited medications or vaccinations outlined in the exclusion criteria (Section 6.2) are not permitted during the course of this trial. If there is a clinical indication for one of these prohibited medications or vaccinations, the patient must be discontinued from trial therapy. The Qualified Investigator must discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination is at the discretion of the Qualified Investigator and/or the subject's primary physician.

6.4.1 Acceptable Concomitant Medications

All treatments at the discretion of the Qualified Investigator that is considered necessary for the subject's welfare may be administered as per the site's institutional standards and guidelines. All concomitant medication must be recorded on the patient's CRF including all prescription, over-the-counter (OTC), and herbal supplements.

All concomitant medications received within 28 calendar days before the first dose of trial treatment and 30 calendar days after the last dose of Pembrolizumab must be recorded in the CRF. Medications administered more than 30 calendar days after the last dose of trial treatment should be recorded for serious adverse events (SAEs) and ECIs. Refer to Section 8.2.1.1 (SAEs) and Section 8.2.1.2 (ECIs).

During the Second Course Phase, record medications received within 28 calendar days prior to the first retreatment dose to 30 calendar days after the last dose of trial treatment. Medications administered more than 30 calendar days after the last dose of trial treatment should be recorded for SAEs and ECIs.

6.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during Screening, the Initial Treatment Period, and the Second Course Phase of this trial:

- Anti-neoplastic 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: Palliative radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Qualified Investigator's discretion once reviewed by the Sponsor.
- Live vaccines within 30 calendar 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, bacillus Calmette-Guerin (BCG), and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than symptom management of a suspected immunologic AE are not permitted. The use of physiologic doses of corticosteroids may be approved only after documented consultation with the Sponsor.

Subjects who, at the discretion of the Qualified Investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from the trial.

The Exclusion Criteria indicates all other medications, which are prohibited in this trial.

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

6.5 Rescue Medications & Supportive Care

6.5.1 Supportive Care Guidelines for Pembrolizumab Immune related Adverse Events

Subjects must receive appropriate supportive care measures as per the site's institutional standards and guidelines deemed necessary by the treating Qualified Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or IV 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 progressive metastatic disease or bacterial or viral infection, which might require additional supportive care. The supportive care guidelines are to be applied when the Investigator determines the events to be related to Pembrolizumab.

Please note as per Table 3, permanently discontinue Pembrolizumab if toxicity does not resolve within 12 weeks or for the inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Supportive Care Guidelines

Pneumonitis Supportive Care Guidelines

Pneumonitis	
CTCAE Grade	
Grade 2	<u>Course of Action:</u> Hold Pembrolizumab <u>Corticosteroid Dosing:</u> Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. (When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks). <u>Additional Information:</u> Add prophylactic antibiotics for opportunistic infections. Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. If a second episode of pneumonitis (Grade 2 or higher) occurs upon re-introduction of study drug—discontinue Pembrolizumab.
Grade 3 or 4	<u>Course of Action:</u> Discontinue Pembrolizumab <u>Corticosteroid Dosing:</u> Immediately treat with IV steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. <u>Anti-Inflammatory Dosing and Additional Corticosteroid Measures:</u> If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed. <u>Additional Information:</u> Add prophylactic antibiotics for opportunistic infections. Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.

Diarrhea/Colitis Supportive Care Guidelines

Diarrhea/Colitis	
CTCAE Grade	
Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool) for no less than 3 days.	<u>Course of Action: Hold Pembrolizumab</u> <u>Symptomatic Treatment:</u> For Grade 2 diarrhea (that may contain blood or mucus) and persists for no less than 3 days treat as per institutional standard of care. <u>Corticosteroid Dosing:</u> Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent) When symptoms resolve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. <u>Additional Information:</u> Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with $\geq$ 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.
Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for greater than 3 days)	<u>Course of Action: Hold Pembrolizumab</u> <u>Corticosteroid Dosing:</u> Treat with Bolus dose of IV corticosteroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding. <u>Anti-Inflammatory Dosing and Additional Corticosteroid Measures:</u> If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as per institutional standard of care. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed. <u>Additional Information:</u> Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with $\geq$ 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.
Grade 4	<u>Course of Action:</u> Permanently discontinue Pembrolizumab and manage symptoms as per Grade 3.

Hypophysitis or Other Endocrinopathy (Excluding thyroid disorders and diabetes) Supportive Care Guidelines

Hypophysitis or other endocrinopathy except hypo-or hyperthyroidism or diabetes	
CTCAE Grade	
Grade 2	<u>Course of Action:</u> Withhold Pembrolizumab until toxicity resolves to Grade 0-1 and corticosteroid has been tapered. <u>Corticosteroid Dosing:</u> Treat with prednisone 40 mg p.o. or equivalent per day, as clinically indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. <u>Hormone Dosing:</u> Replacement of appropriate hormones may be required as the steroid dose is tapered, as clinically indicated. <u>Additional Information:</u> Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
Grade 3-4	<u>Course of Action:</u> Hold <u>or</u> permanently discontinue Pembrolizumab, as per Investigator discretion. <u>Corticosteroid Dosing:</u> IV corticosteroids should be initiated first followed by oral steroid, as clinically indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Other immunosuppressive treatment should be initiated if the drug-related AE cannot be controlled by corticosteroids. <u>Hormone Dosing:</u> Replacement of appropriate hormones may be required as the steroid dose is tapered, as clinically indicated. <u>Additional Information:</u> Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Resume Pembrolizumab when AE resolves to $\leq$ Grade 2 and is controlled with hormonal replacement therapy.

New Onset Diabetes Mellitus (Including Diabetic Ketoacidosis) or Hyperglycemia Supportive Care Guidelines

New Onset Diabetes Mellitus (including diabetic ketoacidosis) or Hyperglycemia	
CTCAE Grade	
T1DM or Grade 3-4 Hyperglycemia	<u>Course of Action:</u> Hold Pembrolizumab <u>Course of Treatment:</u> Insulin replacement therapy is recommended for Type I diabetes mellitus. Administer anti-hyperglycemic in participants with hyperglycemia. As per institutional standards. <u>Additional Information:</u> Monitor participants for hyperglycemia or other signs and symptoms of diabetes. Resume Pembrolizumab when AE resolves to $\leq$ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Hypo- or Hyperthyroidism Supportive Care Guidelines

Hypo- or Hyperthyroidism	
CTCAE Grade	
Grade 2 hyperthyroidism or Grade 2-4 hypothyroidism	<u>Course of Action:</u> Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted. Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. <u>Course of Treatment:</u> Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency as per institutional standards. <u>Course of Treatment in Hyperthyroidism:</u> Non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate. <u>Course of Treatment in Hypothyroidism:</u> Thyroid hormone replacement therapy, with levothyroxine or liothyronine, as per institutional standards. <u>Additional Information:</u> Monitor for signs and symptoms of thyroid disorders.
Grade 3-4 hyperthyroidism	<u>Course of Action:</u> Hold or permanently discontinue Pembrolizumab, as per Investigator discretion <u>Course of Treatment in Hyperthyroidism:</u> Non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate. <u>Additional Information:</u> Monitor for signs and symptoms of thyroid disorders. Resume Pembrolizumab when AE resolves to $\leq$ Grade 2 and is controlled with hormonal replacement therapy.

Hepatic Supportive Care Guidelines

Hepatic Drug Induced Liver Injury (DILI) The event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as: 1. An elevated ALT or AST lab value that is greater than or equal to three times (3X) the ULN and 2. An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and 3. At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN, 4. As a result of within-protocol-specific testing or unscheduled testing. Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.
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CTCAE Grade	
Grade 2	<u>Course of Action:</u> Hold Pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN. <u>Corticosteroid Dosing:</u> Treat with 0.5-1 mg/kg/day of methylprednisolone or oral equivalent and when Liver Function Tests return to grade 1 or baseline, taper steroids over at least 1 month, and resume Pembrolizumab per protocol. <u>Additional Information:</u> Permanently discontinue Pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases $\geq 50\%$ relative to baseline and lasts ≥ 1 week. Monitor with liver function tests (consider weekly or more frequently) until liver enzyme value returned to baseline or is stable
Grade 3	<u>Course of Action:</u> Permanently discontinue Pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN. <u>Corticosteroid Dosing:</u> Treat with high-dose IV glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg/day should be started and continued over no less than 4 weeks. If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity. <u>Additional Information:</u> Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. Monitor with liver function tests (consider weekly or more frequently) until liver enzyme value returns to baseline or is stable
Grade 4	<u>Course of Action:</u> Permanently discontinue Pembrolizumab. Manage patient as per Grade 3 above.

Renal Dysfunction or Nephritis Supportive Care Guidelines

Renal Dysfunction or Nephritis	
CTCAE Grade	
Grade 2	<u>Course of Action:</u> Hold Pembrolizumab when creatinine > 1.5 to ≤ 3 times ULN. <u>Corticosteroid Dosing:</u> Treatment with prednisone 1-2 mg/kg p.o. daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. <u>Additional Information:</u> Monitor for changes in renal function
Grade 3-4	<u>Course of Action:</u> Discontinue Pembrolizumab when creatinine > 3 times ULN. <u>Corticosteroid Dosing:</u> Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Other immunosuppressive treatment should be initiated if the drug-related AE cannot be controlled by corticosteroids. <u>Additional Information:</u> Monitor for changes in renal function

Myocarditis Supportive Care Guidelines

Myocarditis	
- Ensure adequate evaluation to confirm etiology and/or exclude other causes	
CTCAE Grade	
Grade 1-2	<u>Course of Action:</u> Hold Pembrolizumab <u>Corticosteroid Dosing:</u> Treat with corticosteroids based on severity of AE. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
Grade 3-4	<u>Course of Action:</u> Discontinue Pembrolizumab <u>Corticosteroid Dosing:</u> IV corticosteroids should be initiated first followed by oral steroid, as clinically indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Other immunosuppressive treatment should be initiated if the drug-related AE cannot be controlled by corticosteroids.

Skin Reactions Supportive Care Guidelines

Skin Reactions	
- Monitor for suspected severe skin reactions and exclude other causes	
CTCAE Grade	
Grade 3 or suspected SJS or TEN	<u>Course of Action: Hold Pembrolizumab</u> <u>Corticosteroid Dosing:</u> IV corticosteroids should be initiated first followed by oral steroid, as clinically indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Other immunosuppressive treatment should be initiated if the drug-related AE cannot be controlled by corticosteroids.
Grade 4 or confirmed SJS or TEN	<u>Course of Action: Discontinue Pembrolizumab</u> <u>Corticosteroid Dosing:</u> IV corticosteroids should be initiated first followed by oral steroid, as clinically indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Other immunosuppressive treatment should be initiated if the drug-related AE cannot be controlled by corticosteroids.

Infusion Reactions Supportive Care Guidelines

Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs and symptoms can include: rigors, chills, fever, wheezing, pruritis, flushing, rash, hypotension, and hypoxemia.		
CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> 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
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (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 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

[illegible]

All Other Drug-Related Toxicity	
-Ensure adequate evaluation to confirm etiology and/or exclude other causes	
CTCAE Grade	
Intolerable/persistent Grade 2	<u>Course of Action:</u> Hold Pembrolizumab <u>Corticosteroid Dosing:</u> Treat with corticosteroids based on severity of AE. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
Grade 3	<u>Course of Action:</u> Hold <u>or</u> permanently discontinue Pembrolizumab, based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis <u>Corticosteroid Dosing:</u> IV corticosteroids should be initiated first followed by oral steroid, as clinically indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Other immunosuppressive treatment should be initiated if the drug-related AE cannot be controlled by corticosteroids.

CTCAE Grade	
Grade 4 or recurrent Grade 3	Course of Action: Discontinue Pembrolizumab Corticosteroid Dosing: IV corticosteroids should be initiated first followed by oral steroid, as clinically indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Other immunosuppressive treatment should be initiated if the drug-related AE cannot be controlled by corticosteroids.

6.6 Diet/Activity/Other Considerations

6.6.1 Diet

Subjects should maintain a normal diet unless modifications are required, as per the discretion of the treating Qualified Investigator to manage an AE such as diarrhea, nausea or vomiting.

6.6.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. It is unknown 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 (see Inclusion Criteria in Section 6.1) 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 two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects must start using birth control from the time they have signed the Informed Consent Form prior to start of therapy until 120 calendar days post completion of study therapy or study discontinuation.

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 might 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 8.2.1.3 – 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.

6.6.3 Pregnancy

If a subject becomes pregnant while on treatment with Pembrolizumab, the subject will immediately be discontinued from the study. The site is required to report the pregnancy to the Sponsor within 24 hours of becoming aware. The site is required to contact the subject at a minimum of once a month to assess the status of the pregnancy. The site is required to document the subject's pregnancy status in the CRF until the pregnancy is complete or terminated, whichever comes first. The outcome of the pregnancy will be reported to the **Sponsor** within 24 hours who will in turn report this, within 2 working days, to Merck Canada Inc. Safety (see Section 8.2.1.3).

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 followed as described above and in Section 8.2.1.3.

6.6.4 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.

6.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time, for any reason or may be discontinued from the trial at the discretion of the Qualified Investigator. In addition, a subject may be withdrawn from trial by the Sponsor for any safety reason the Sponsor deems to be a significant risk to the trial participant(s) or for trial noncompliance on the part of either the participants themselves or the site involved. The Sponsor may stop the study if trial enrollment is not being met appropriately. Specific details regarding discontinuation or withdrawal are provided in Section 8.1.4 – Other Procedures.

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

- Confirmed and documented radiographic disease progression as per RECIST® 1.1.
Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 8.1.2.5.
- Unacceptable toxicities as described in Section 6.3.1.2.
- Intercurrent illness that prevents further administration of treatment
- Investigator's documented 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. A subject is considered lost to follow-up if 2 documented attempts, made at least 3 weeks apart, were unsuccessful.
- Completed either 24 calendar months of uninterrupted treatment with Pembrolizumab or a total of 35 administrations of Pembrolizumab, whichever is later.

Note: 24-calendar months of study medication is calculated from the date of first dose (Day 1). Subjects who stop Pembrolizumab after 24 calendar months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 8.1.5.5.

The End of Treatment and Follow-Up Visit procedures are listed in Section 7.0 (Trial Flow Charts) and Section 8.1.5 (Visit Requirements). AEs will be collected until the Safety Follow-Up Visit (30 days $\pm$ 7 calendar days post last dose). SAEs will be collected for 90 calendar days post last dose of trial medication if no new treatments have been started. SAEs will be collected for 30 days post last dose of trial medication if a new treatment is started (refer to Section 8.2.1.1). Subjects who discontinue for reasons other than PD will have post-treatment Follow-Up every 9 weeks for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. Once disease progression is confirmed and documented, each participant will be followed by telephone or in person every 12 weeks for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.7.1 Discontinuation of Study Therapy after Complete Response (CR)

Discontinuation of treatment may be considered for subjects who have a documented confirmed CR, have been treated for at least 24 weeks with Pembrolizumab, and had at least two treatments with Pembrolizumab beyond the date when the initial CR was confirmed. Otherwise, subjects with a confirmed CR can continue to receive study treatment in the Initial Treatment Period or in the Second Course Phase (see Section 7.0 – Trial Flow Charts).

Subjects who stop treatment then experience radiographic disease progression may be eligible for up to one year of additional treatment with Pembrolizumab through the Second Course Phase (Section 8.1.5.5), at the discretion of the Qualified Investigator, approval from the Sponsor, and if no other cancer treatment was administered since the last dose of Pembrolizumab, the subject meets the safety parameters listed in the inclusion/exclusion criteria, and the trial is open to accrual. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details regarding the Second Course Phase are provided in Section 8.1.5.5.

6.8 Subject Replacement Strategy

Subjects enrolled will be replaced if they are considered not evaluable for response (e.g. did not receive study treatment, or if they discontinued from study treatment before completion of a response evaluation period (at 9 weeks) for reasons other than safety or a dose-limiting toxicity).

6.9 Clinical Criteria for Early Trial/Site Termination

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

- 1) Quality or quantity of collected data recording is inaccurate or incomplete.
- 2) Poor adherence to protocol and regulatory requirements.
- 3) Any incidence or serious adverse reaction related to Pembrolizumab in this study or any other studies using Pembrolizumab, which suggests a potential severe health risk to trial participants.

In the event that Merck would decide to no longer supply study drug, sufficient notification will be provided to all participating sites by the Sponsor, to ensure appropriate adjustments to any and all subject's treatment can be made.

7.0 TRIAL FLOW CHARTS

7.1 Initial Treatment with Study Drug

Trial Period:	Screening Phase		Treatment Cycles (each cycle is 21 calendar days)									End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Main Study Screening		1	2	3	4	To be repeated beyond 8 cycles				Confirm eligibility for Second Course Phase (see flow chart in Section 7.2) ²	Discontinuation	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
							5	6	7	8					
Week			0	3	6	9	12	15	18	21		At time of Discontinuation	30 days post discontinuation	Every 9 weeks post discontinuation	Every 12 weeks post disease progression
Scheduling Window (Calendar Days):	-28 to -1	-7 to -1		± 3								± 7days			
Administrative Procedures															
Informed Consent ¹	X														
Inclusion/Exclusion Criteria ²	X														
Registration (within 3 days prior to Day 1)		X													
Demographics and Medical History ³	X														
Prior and Concomitant Medication Review ⁴	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Trial Treatment Administration			X	X	X	X	X	X	X	X					
Post-study systemic anti-cancer therapy status															X
Survival Status															X
Clinical Procedures/Assessments															

Trial Period:	Screening Phase		Treatment Cycles (each cycle is 21 calendar days)									End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Main Study Screening		1	2	3	4	To be repeated beyond 8 cycles				Confirm eligibility for Second Course Phase (see flow chart in Section 7.2) ²	Discontinuation	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
							5	6	7	8					
Week			0	3	6	9	12	15	18	21		At time of Discontinuation	30 days post discontinuation	Every 9 weeks post discontinuation	Every 12 weeks post disease progression
Scheduling Window (Calendar Days):	-28 to -1	-7 to -1		± 3									± 7days		
Review Adverse Events ⁵	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Review Serious Adverse Events ⁶		X	X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination ⁷		X	X	X	X	X	X	X	X	X		X	X	X	
Height		X													
Vital Signs and Weight ⁸		X	X	X	X	X	X	X	X	X		X	X	X	
ECOG Performance Status		X	X	X	X	X	X	X	X	X		X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum β-hCG ⁹		X													
PT/INR and aPTT ¹⁰		X		X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰		X ¹⁰	X		
CBC with Differential		X		X	X	X	X	X	X	X		X	X	X	
Serum Chemistry Panel ¹¹		X		X	X	X	X	X	X	X		X	X	X	
Calculated Creatinine Clearance ¹² and Cortisol ¹³		X		X ^{12,13}	X ^{12,13}	X ^{12,13}	X ^{12,13}	X ^{12,13}	X ^{12,13}	X ^{12,13}		X ^{12,13}	X ^{12,13}	X ^{12,13}	
Urinalysis ¹⁴		X					X					X			
T3, FT4 and TSH ¹⁵		X		X	X	X		X		X		X			

Trial Period:	Screening Phase		Treatment Cycles (each cycle is 21 calendar days)									End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Main Study Screening		1	2	3	4	To be repeated beyond 8 cycles				Confirm eligibility for Second Course Phase (see flow chart in Section 7.2) ²	Discontinuation	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
						5	6	7	8						
Week			0	3	6	9	12	15	18	21		At time of Discontinuation	30 days post discontinuation	Every 9 weeks post discontinuation	Every 12 weeks post disease progression
Scheduling Window (Calendar Days):	-28 to -1	-7 to -1		± 3							± 7days				
Efficacy Measurements															
CT or MRI Tumor Imaging ¹⁶	X					X			X					X	
Tumor Biopsies/Archival Tissue Collection															
Archival or Newly Obtained Tissue Collection ¹⁷	X														

- Written informed consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 calendar days prior to Cycle 1, Day 1). An additional consent is required entitled “Re-Initiation of Treatment Upon Disease Progression”, if patient is undergoing the Second Course Phase (Section 8.1.5.5).
- If undergoing the Second Course Phase the conditions from section 8.1.5.5 must be met. Refer to Trial Flow Chart in Section 7.2 – Second Course Phase.
- Demographics includes age, gender, and race. Medical history includes information on relevant past medical history, current conditions, recent illnesses, and a history of allergies. Past medical history includes any condition diagnosed within the prior

10 years that are considered clinically significant by the Qualified Investigator. Medical history also includes history of treatment for CUP, including radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the Investigator.

4. Medications administered more than 30 calendar days after the last dose of trial treatment should be recorded for SAEs and ECIs. Refer to Section 6.4.1.
5. Collect all AEs starting as soon as the informed consent is signed. The Investigator must review AEs prior to registration to confirm subject meets eligibility criteria. After the Safety Follow-Up Visit, continue to follow AEs of Grade > 1 until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Refer to Section 8.2 - Assessing and Recording Adverse Events. Also refer to Section 8.2.1.2 for details on select AEs that need to be reported within 24 hours.
6. Collect SAEs from the first dose of Pembrolizumab in the Initial Treatment Period to 90 days post last dose, or 30 days post last dose if the subject initiates a new anti-cancer therapy. Only select SAEs are reported from registration to the first dose. Refer to Section 8.2.1.1 for details. ECIs will be collected throughout the study as listed in Section 8.2.1.2.
7. The physical exam includes a review of all body organ systems. Include genitourinary only if symptomatic.
8. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
9. For women of reproductive potential, a urine or serum pregnancy test will be performed within 7 calendar days of the first dose of Pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Patients of reproductive potential must agree to use contraception as per Section 6.6.2.
10. PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-Up Visit after discontinuation of study therapy. Repeat coagulation parameters from Cycle 2 (Week 3) to the End of Treatment Visit if clinically indicated.
11. The Chemistry Panel includes albumin, ALP, ALT, AST, lactate dehydrogenase (LDH), bicarbonate, uric acid, calcium, chloride, random glucose, phosphorous, potassium, sodium, magnesium, total bilirubin, total protein, blood urea nitrogen and serum creatinine. Direct bilirubin is only required if total bilirubin is elevated above the ULN. Please refer to Table 4 – Laboratory Tests.
12. Repeat calculated creatinine clearance, if clinically indicated, from Cycle 2 (Week 3) to the Follow-Up Visits. As per Cockcroft and Gault formula found in Section 12.4.
13. Repeat cortisol, if clinically indicated, from Cycle 2 (Week 3) to the Follow-Up Visits.
14. Following screening, urinalysis should be performed every 12 weeks.
15. Following Cycle 4, analysis of total triiodothyronine (T3), free thyroxine (T4 or FT4) and thyroid stimulating hormone

(TSH) will be performed every other cycle.

16. Ideally, baseline tumor imaging should be performed within 28 days of first treatment, but baseline scans within 42 days of first treatment will be acceptable. Radiological tumor assessment will be performed every 9 weeks (± 7 calendar days) after start of treatment, unless clinically indicated. Confirm CR by a repeat tumor assessment obtained 4 weeks or longer from the date the initial CR was first documented. The tumor imaging performed to confirm a response may be performed, at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan [i.e., 9 weeks later (63 days ± 7 days)], whichever is clinically indicated. At first radiographically suspected disease progression during the Initial Treatment Period, a confirmatory radiographic scan is required at least 4 weeks from the date of the initial PD scan. A confirmatory scan is not needed during the every 9 week Follow-Up period in order for a patient to be eligible for the Second Course Phase. Refer to section 8.1.2.5 – Tumor Imaging and Assessment of Disease.
17. Collection of tumor tissue is mandatory in this study. Tumor tissue samples from a newly obtained core or excisional biopsy are preferred. Newly obtained is defined as a specimen obtained up to 6 weeks (42 calendar days) prior to initiation of treatment on Day 1. If a patient is unable to provide a newly obtained tumor biopsy, then collection of archival tissue is required. If a patient has multiple archival tumor tissue samples, the most recently obtained sample is preferred. A patient does not need to wait to enter the study while the archival tumor specimen is being obtained.

7.2 Second Course Phase

Trial Period:	Screening Phase		Treatment Cycles (each cycle is 21 calendar days)								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening for Second Course Phase		1	2	3	4	To be repeated beyond 8 cycles				Discontinuation	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
							5	6	7	8				
Week	Starts at signing of the informed consent ¹		0	3	6	9	12	15	18	21	At time of Discontinuation	30 days post discontinuation	Every 9 weeks post discontinuation	Every 12 weeks post disease progression
Scheduling Window (Calendar Days):	-28 to -1	-7 to -1		± 3							± 7days			
Administrative Procedures														
Informed Consent ¹	X													
Inclusion/Exclusion Criteria ²	X													
Registration (within 3 days prior to Day 1)		X												
Prior and Concomitant Medication Review ³	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Treatment Administration			X	X	X	X	X	X	X	X				
Post-study systemic anti-cancer therapy status														X
Survival Status														X
Clinical Procedures/Assessments														
Review Adverse Events ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Serious Adverse Events ⁵		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination ⁶		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight ⁷		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-hCG ⁸		X												

Trial Period:	Screening Phase		Treatment Cycles (each cycle is 21 calendar days)								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening for Second Course Phase		1	2	3	4	To be repeated beyond 8 cycles				Discontinuation	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
							5	6	7	8				
Week	Starts at signing of the informed consent ¹		0	3	6	9	12	15	18	21	At time of Discontinuation	30 days post discontinuation	Every 9 weeks post discontinuation	Every 12 weeks post disease progression
Scheduling Window (Calendar Days):	-28 to -1	-7 to -1		± 3							± 7days			
PT/INR and aPTT ⁹		X		X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X		
CBC with Differential		X		X	X	X	X	X	X	X	X	X	X	
Serum Chemistry Panel ¹⁰		X		X	X	X	X	X	X	X	X	X	X	
Calculated Creatinine Clearance ¹¹ and Cortisol ¹²		X		X ^{11,12} ₂	X ^{11,12} ₂	X ^{11,12} ₂	X ^{11,12}	X ^{11,12}	X ^{11,12}	X ^{11,12}	X ^{11,12}	X ^{11,12}	X ^{11,12}	
Urinalysis ¹³		X					X				X			
T3, FT4 and TSH ¹⁴		X		X	X	X		X		X	X			
Efficacy Measurements														
CT or MRI Tumor Imaging ¹⁵	X					X			X				X	

1. An additional written informed consent, entitled “Re-Initiation of Treatment Upon Disease Progression”, must be obtained prior to performing any protocol specific procedure in the Second Course Phase. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.
2. The conditions from section 8.1.5.5 must be met in order to be eligible for the Second Course Phase.
3. Medications administered more than 30 calendar days after the last dose of trial treatment should be recorded for SAEs and ECIs. Refer to Section 6.4.1.
4. Collect all AEs starting as soon as the informed consent is signed. The Investigator must review AEs prior to registration to confirm subject meets eligibility criteria. After the Safety Follow-Up Visit, continue to follow AEs of Grade > 1 until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Refer to Section 8.2 - Assessing and Reporting Adverse Events.
5. Collect SAEs from the first dose of Pembrolizumab in the Second Course Phase to 90 days post last dose, or 30 days post last

dose if the subject initiates a new anti-cancer therapy. Only select SAEs are reported from registration to the first dose. Refer to Section 8.2.1.1 for details. ECIs will be collected throughout the study as listed in Section 8.2.1.2.

6. The physical exam includes a review of all body organ systems. Include genitourinary only if symptomatic.
7. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
8. For women of reproductive potential, a urine or serum pregnancy test will be performed within 7 calendar days of the first dose of Pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Patients of reproductive potential must agree to use contraception as per Section 6.6.2.
9. PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-Up Visit after discontinuation of study therapy. Repeat coagulation parameters from Cycle 2 (Week 3) to the End of Treatment Visit if clinically indicated.
10. The Chemistry Panel includes albumin, ALP, ALT, AST, LDH, bicarbonate, uric acid, calcium, chloride, random glucose, phosphorous, potassium, sodium, magnesium, total bilirubin, total protein, blood urea nitrogen and serum creatinine. Direct bilirubin is only required if total bilirubin is elevated above the ULN. Please refer to Table 4 – Laboratory Tests.
11. Repeat calculated creatinine clearance, if clinically indicated, from Cycle 2 (Week 3) to the Follow-Up Visits. As per Cockcroft and Gault formula found in Section 12.4.
12. Repeat cortisol, if clinically indicated, from Cycle 2 (Week 3) to the Follow-Up Visits.
13. Following screening, urinalysis should be performed every 12 weeks.
14. Following Cycle 4, Analysis of T3, FT4 and TSH will be performed every other cycle.
15. Ideally, baseline Second Course Phase tumor imaging should be performed within 28 days of first dose of study drug, but baseline scans within 42 days of first dose will be acceptable. Radiological tumor assessment will be performed every 9 weeks (+/- 7 calendar days) after start of treatment, unless clinically indicated. Confirm CR by a repeat tumor assessment obtained 4 weeks or longer from the date the initial CR was first documented. The tumor imaging performed to confirm a response may be performed, at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan [i.e., 9 weeks later (63 days $\pm$ 7 days)], whichever is clinically indicated. At first radiographically suspected disease progression while the patient is on treatment, a confirmatory radiographic scan is required at least 4 weeks from the date of the initial PD scan. A confirmatory scan is not needed during the every 9 week Follow-Up period unless clinically indicated. Please refer to section 8.1.2.5 – Tumor Imaging and Assessment of Disease.

8.0 TRIAL PROCEDURES

8.1 Trial Procedures

The Trial Flow Charts - Section 7.0 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.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

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

8.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative'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 must be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent forms and any written information provided to the subject must receive REB approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative 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 or by the subject's legally acceptable representative's dated signature.

Specifics about the trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to REB requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 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.

8.1.1.3 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 Qualified Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and are required to be listed as medical history.

8.1.1.4 Prior and Concomitant Medications Review

8.1.1.4.1 Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirements, and document prior medication taken by the subject within 28 calendar days prior to the first dose of study medication.

8.1.1.4.2 Concomitant Medications

The investigator or qualified designee will document all medication taken by the subject from the first dose of trial treatment to 30 days after the last dose of trial treatment. All medications related to reportable SAEs should be recorded. Medications administered more than 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs. Refer to Section 8.2.1.1 (SAEs) and Section 8.2.1.2 (ECIs).

During the Second Course Phase, record medications received within 28 calendar days prior to the first retreatment dose to 30 calendar days after the last dose of trial treatment. Medications administered more than 30 calendar days after the last dose of trial treatment should be recorded for SAEs and ECIs.

8.1.1.5 Disease Details and Treatments

8.1.1.5.1 Disease Details

The Investigator or qualified designee will obtain details regarding disease status as per RECIST® 1.1.

8.1.1.5.2 Prior Treatment Details

The Investigator or qualified designee will review all prior cancer treatments received for CUP, including radiation and surgeries.

8.1.1.5.3 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 calendar days after the last dose of trial medication, the 30-day Safety Follow-Up visit must occur prior to the initiation of the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into Survival Follow-Up, as per Trial Flow Charts (Section 7.0).

8.1.1.6 Assignment of Subject Number

A subject identification number will be assigned once eligibility is confirmed by the Sponsor. The subject identification number will consist of the single digit site number followed by a hyphen and then a unique identifier, for example 1-001.

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

The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Adverse Event Monitoring

The Investigator or qualified designee will assess each subject for any potential new or worsening AEs as specified in the Trial Flow Charts, Section 7.0. AEs will be graded and recorded throughout the duration of the study and during the Follow-Up period according to NCI CTCAE Version 4.0 (see Section 12.2). AE documentation will include seriousness, causality, grade, action taken, and start and stop dates.

Please refer to section 8.2 for detailed information regarding the assessment and documenting of AEs.

8.1.2.2 Physical Exam

The Investigator or qualified designee is required to perform and document a physical exam during the screening period. Clinically significant abnormal physical exam findings should be

documented as AEs. A physical exam should be performed as per the Trial Flow Charts, Section 7.0. Each physical exam must include a review of all body organ systems. Include genitourinary only if symptomatic.

8.1.2.3 Vital Signs

The Investigator or qualified designee is required to collect and document vital signs as specified in the Trial Flow Charts (Section 7.0). Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height is required to be measured at screening only.

8.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess and document ECOG status (see Section 12.1) as specified in the Trial Flow Charts (Section 7.0).

8.1.2.5 Tumor Imaging and Assessment of Disease

The RECIST[®] 1.1 criteria are the primary measure for assessment of tumor and disease status throughout the duration of this study (e.g., discontinuation of study therapy). The Investigator will perform disease response assessments with interpretation of the scans by the site radiologist.

After radiological tumor assessment at Screening, the first radiological assessment of tumor response status will be performed at Week 9 (± 7 calendar days), unless there is clinical indication based on the discretion of the Investigator warranting earlier radiologic imaging (see Section 7.0 – Trial Flow Charts). The same imaging technique as used at Screening should be used throughout the study.

While a patient is on study treatment (during the Initial Treatment Period or the Second Course Phase), CR should be confirmed by a repeat tumor assessment at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan [i.e., 9 weeks later (63 days ± 7 days)], whichever is clinically indicated.

If imaging at Week 9 suggests PD, it is at the discretion of the Investigator to keep a patient on study treatment or to discontinue study treatment until repeat imaging is performed at least 4 weeks from the date of the initial scan to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory results. If repeat imaging indicates an objective response or stable disease relative to baseline, treatment with Pembrolizumab will continue/resume and the next imaging studies will be conducted approximately at Week 18, and every 9 weeks subsequently.

The same paradigm for confirmatory scans of progression of disease at least 4 weeks after the initial finding is only applicable to subsequent planned scanning intervals while a patient is on study treatment.

If a scan shows disease progression as per Investigator discretion during a Follow-Up Visit (performed every 9 weeks post discontinuation), repeat imaging is only needed if it is clinically indicated. If a single scan performed in this Follow-Up period shows disease progression as per Investigator discretion, the patient may be eligible for the Second Course Phase (Section 8.1.5.5).

8.1.2.6 Tumor Tissue Collection

Collection of tumor tissue is mandatory in this study, as the investigation of predictive candidate biomarkers is an important study objective. Tumor tissue samples from a newly obtained core or excisional biopsy are preferred. Newly obtained is defined as a specimen obtained up to 6 weeks (42 calendar days) prior to initiation of treatment on Day 1 of the Initial Treatment Period. If a patient is unable to provide a newly obtained tumor biopsy, then collection of archival tumor tissue is required. If a patient has multiple archival tumor tissue samples, the most recently obtained tissue sample is preferred. A patient does not need to wait to enter the study while the archival tumor specimen is being obtained. Refer to the QualTek Sample Handling Manual.

8.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided in Table 4 on page 49.

Table 4 Laboratory Tests

Hematology and Coagulation	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β -human chorionic gonadotropin (β -hCG) ^a
Hemoglobin	Alkaline phosphatase (ALP)	Glucose	
Platelet count	Alanine aminotransferase (ALT)	Protein	Total triiodothyronine (T3)
White blood cells (WBC) (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (T4 or FT4)
	Lactate dehydrogenase (LDH)	Microscopic exam (<i>If abnormal results are noted</i>)	Thyroid stimulating hormone (TSH)
Red Blood Cell Count	Bicarbonate		Calculated creatinine clearance ^b
Absolute Neutrophil Count	Uric Acid	Urine pregnancy test ^a	Cortisol
Absolute Lymphocyte Count	Calcium		
	Chloride		
PT or INR	Random glucose		
aPTT	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is elevated above the ULN</i>)		
	Total protein		
	Blood Urea Nitrogen		
	Serum creatinine		

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

b. As per Cockcroft and Gault Formula (Section 12.4).

Laboratory tests for screening or entry into the Second Course Phase (Section 8.1.5.5) should be performed within 7 calendar days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

8.1.4 Other Procedures

8.1.4.1 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 AEs, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events. Withdrawal/Discontinuation as it relates to this study can be defined as follows:

- Withdrawal from active study treatment/procedures while maintaining active data collection
- Withdrawal from study and data collection
- Discontinuation from main study but eligible for Second Course Phase
 - *Subjects who stop Pembrolizumab with stable disease (SD), partial response (PR), or CR are eligible for up to one year of additional Pembrolizumab therapy if they have radiographical or clinical evidence of disease progress after stopping Pembrolizumab and meet the conditions listed in Section 8.1.5.5.*

8.1.5 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Charts. Specific procedure-related details are provided above in Section 8.1 - Trial Procedures.

8.1.5.1 Screening

8.1.5.1.1 Screening Period

Subjects will be screened for eligibility between -28 and -1 days prior to the first day of treatment with Pembrolizumab.

Refer to Trial Flow Charts (Section 7.0) for the evaluations that will be performed to assess the subject's eligibility for the study. Assessments may occur over the course of multiple days within the screening period. AE reporting will commence as soon as the informed consent is signed.

Subject's extent of disease will be determined prior to start of Pembrolizumab using the screening physical exam and routine radiologic and laboratory assessments.

8.1.5.2 Treatment Period

Once the subject has been confirmed eligible for study, the subject must begin the study treatment within 28 calendar days of signing the informed consent and 7 days of the baseline laboratory investigations, in either the Initial Treatment Period or the Second Course Phase. For all subsequent cycles, Day 1 visits can occur +/- 3 calendar days of the scheduled visit.

At the start of every visit during the treatment period refer to Trial Flow Charts (Section 7.0) for all required assessments.

8.1.5.3 Post-Treatment Visits

8.1.5.3.1 End of Treatment Visit

At time of discontinuation see Trial Flow Charts (Section 7.0) for End of Treatment procedures. Subjects who are eligible for retreatment with Pembrolizumab (as described in Section 8.1.5.5) may have up to two End of Treatment visits, one after the Initial Treatment Period and one after the Second Course Phase.

8.1.5.3.2 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit must be conducted 30 days (+/- 7 calendar days) after the last dose of trial treatment or before the initiation of a new anti-neoplastic treatment, whichever comes first. All AEs that occur from the time the informed consent is signed to the Safety Follow-Up Visit should be recorded. Subjects with an AE 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 calendar days post last dose or within 30 calendar days post last dose if the subject initiates a new anti-cancer therapy, whichever is earlier, should also be followed and documented in the CRF.

Subjects who are eligible for retreatment with Pembrolizumab (as described in Section 8.1.5.5) may have up to two Safety Follow-Up visits, one after the Initial Treatment Period and one after the Second Course Phase.

8.1.5.4 Follow-Up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up period and should be assessed every 9 weeks (63 ± 7 calendar days) as per Trial Flow Charts (Section 7.0). 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 or if the subject begins retreatment with Pembrolizumab as detailed in Section 8.1.5.5. Information regarding post-study systemic anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with Pembrolizumab according to the criteria in Section 8.1.5.5 will move from the Follow-Up period to the Second Course Phase only at disease progression.

This Follow-Up period also applies to subjects who discontinue trial treatment in the Second Course Phase for a reason other than disease progression.

8.1.5.4.1 Survival Follow-Up

Once a subject has a confirmed and documented disease progression or starts a new anti-cancer therapy, after receiving study treatment in the Initial Treatment Period or Second Course Phase, the subject will move into the Survival Follow-Up phase. The subject is required to be contacted for survival status by telephone or in person every 12 weeks (+/- 7 calendar days) until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.1.5.5 Second Course Phase

Subjects who stop Pembrolizumab with SD, PR, or CR are eligible for up to one year of additional Pembrolizumab therapy if they have radiographical or clinical evidence of disease progression after stopping Pembrolizumab. This is the Second Course Phase of this study and will only be available if the study remains open and the subject meets the following conditions:

- **Either**

- Stopped initial treatment with Pembrolizumab after a confirmed CR as per RECIST[®] 1.1, and
 - Was treated for at least 24 weeks with Pembrolizumab before discontinuing therapy
 - Received at least two treatments with Pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and discontinued Pembrolizumab after 24 months for reasons other than disease progression or intolerability

AND

- Experienced a confirmed radiographic disease progression after stopping initial treatment with Pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of Pembrolizumab
- Has a ECOG performance status of 0 to 1 on the ECOG Performance Scale

- Demonstrates adequate organ function as detailed in Section 6.1.
- Female subject of childbearing potential has a documented negative serum or urine pregnancy test within 7 calendar days prior to receiving retreatment with Pembrolizumab.
- Female subject of childbearing potential are 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 calendar days after the last dose of study medication. Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
- Male subject must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 calendar days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
- Has not received any chemotherapies or other treatments after the initial treatment with Pembrolizumab.

Subjects who restart treatment will begin at the same dose and dose interval as when they last received Pembrolizumab. Treatment will be administered for up to one additional 12 calendar months.

Visit requirements are outlined in Section 7.2 – Second Course Phase, however an additional consent is required entitled “Re-Initiation of Treatment Upon Disease Progression”.

8.2 Assessing and Recording Adverse Events

An AE 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 AE 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 Pembrolizumab is also an AE.

AEs may occur during the course of the use of Pembrolizumab in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an AE.

8.2.1 Immediate Reporting of Serious Adverse Events and Events of Clinical Interest

All SAEs and those events deemed ECIs must be reported in an expedited manner using the Merck Global Safety Intake Form following the schedule outlined below to:

Dr. Jose Monzon, MD FRCPC
Study Chair
Tom Baker Cancer Centre, 1331, 29th St NW
Calgary, Alberta Canada T2N 4N2
Telephone: 403-521-3688
Fax: 403-283-1651
Email: jose.monzon@albertahealthservices.ca

- ***Within 24 hours:*** SAEs are reported by fax to the Sponsor (Dr. Jose Monzon). An initial SAE Form is also scanned and emailed to Dr. Jose Monzon and the Lead Study Coordinator. As much information at the time should be included.
- ***Within 5 working days:*** An SAE Form is completed with any further information and faxed to Dr. Jose Monzon. An SAE Form is also scanned and emailed to Dr. Jose Monzon and the Lead Study Coordinator. As much information as is available at the time should be included.

All SAEs and ECIs, must be recorded on the CRF. Ensure that the information recorded on the Global Safety Intake Form is correctly reflected on the Adverse Event Log CRF and additional CRFs, as appropriate.

In the event that the Investigator does not become aware of the occurrence of an SAE immediately (for example, if an outpatient clinical trial subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the date of first awareness of the event.

SAE Reports will be forwarded to the company whose drug is being utilized in the study (Merck Canada) by the Sponsor.

Health Canada and collaborating centers will be notified by the Sponsor in an expedited manner of all SAEs which are unexpected and related to the investigational product.

Merck Reporting Requirements

For patients exposed to Pembrolizumab, SAE and Suspected Unexpected Serious Adverse Reaction (SUSAR) reports will be sent by the **Sponsor** to Merck Canada Inc. Safety Fax: 1-800-369-3090.

- Related SAEs and SUSARs

SAE reports that are related to the product will be transmitted by the Sponsor to Merck Canada Inc. Safety within 2 working days of the Sponsor learning of the SAE or SUSAR.

- Unrelated SAEs and SUSARs

SAE reports that are unrelated to the product will be reported by the Sponsor to Merck Canada Inc. Safety within 2 working days of the Sponsor learning of the SAE or SUSAR.

8.2.1.1 Serious Adverse Events

An SAE is any AE 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 clinically significant medical event

Refer to Table 5 for additional details regarding each of the above criteria.

For the time period beginning from registration to treatment, any SAE, or follow up to an SAE, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning from the first dose of study treatment through 90 calendar days following cessation of treatment, or 30 days (+/- 7 calendar days) following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier, any SAE, or follow up to an SAE, including death due to any cause other than progression of the cancer under study, whether or not thought to be related to Pembrolizumab, must be reported within 24 hours to the Sponsor.

Additionally, any SAE, thought to be or to possibly be related to Pembrolizumab at the opinion of the Qualified Investigator at any time following consent to the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported within 24 hours to the Sponsor.

If any SAE is ongoing after 30 or 90 calendar days post last dose, continue to follow the SAE until resolution.

The Sponsor is responsible to report any unexpected fatal or life-threatening SAEs to Health Canada as soon as possible, but no later than 7 calendar days of becoming aware of the event. The Sponsor will report all other serious, unexpected events to Health Canada within 15 calendar days.

The Sponsor is responsible to report any SAEs to Merck Canada Inc. Safety within 2 working days of becoming aware of the event.

8.2.1.2 Events of Clinical Interest

Selected non-serious and serious AEs are also known as ECIs and must be documented as such on the Adverse Event CRFs and reported within 24 hours to the **Sponsor** using the Merck Global Safety Intake Form. The Sponsor will report ECIs within 2 working days to Merck Canada Inc. Safety.

ECIs for this trial include: overdose; drug induced liver injury; and pregnancy.

Subjects should be assessed for possible ECIs from the first dose of Pembrolizumab to 30 calendar days post last dose, with the exception of pregnancies and lactations which may be collected until 120 calendar days post last dose (Section 8.2.1.3). This applies to both the Initial Treatment Period and the Second Course Phase. While subjects are receiving trial treatment, they should be assessed for ECIs 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 ECI thought to be immune-related should have additional testing to rule out other etiologies. If lab results or symptoms suggest a possible immune-related ECI, additional testing should be performed to rule out other causes. If no other cause is identified, it is assumed to be immune-related.

Continue to follow all ECIs until resolution, including ECIs that are ongoing after 30 calendar days post last dose (or 120 calendar days for pregnancies and lactations).

8.2.1.2.1 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 administered of 1,000 mg or greater (≥ 5 times the indicated dose). Currently 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 AE is associated with (“results from”) the overdose of Pembrolizumab, the AE is reported as an SAE, even if no other seriousness criteria are met.

If a dose of Pembrolizumab 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 ECI, using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an AE must be reported within 24 hours to the **Sponsor**. The Sponsor will report the overdose within 2 working days to Merck Canada Inc. Safety.

8.2.1.2.2 Definition and Reporting of Drug Induced Liver Injury to the Sponsor and to Merck

It is the responsibility of Investigators or their designees to report drug induced liver injury as defined below:

- An elevated ALT or AST lab value that is greater than or equal to three times (3X) the ULN and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) the ULN and
- At the same time, an ALP lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event. Such events must be reported within 24 hours to the **Sponsor** who will in turn report this, within 2 working days, to Merck Canada Inc. Safety.

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

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after registration but before treatment must be reported by the Investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment through 120 calendar days following cessation of treatment, or 30 calendar days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier, must be reported by the Investigator. All reported pregnancies 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 SAEs (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** who will in turn report this, within 2 working days, to Merck Canada Inc. Safety.

8.2.1.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 8.2.1, unless there is evidence suggesting a causal relationship between the drug and the event and if deemed an ECI. Any such event will be submitted to the Sponsor within 24 hours, who will in turn forward this information to Merck Canada Inc. Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study. Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

8.2.2 Evaluating Adverse Events

The Qualified Investigator will evaluate all AEs according to the NCI CTCAE Version 4.0. Please note Table 5 below provides guidance for grading AEs not evaluable under CTCAE Version 4.0. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade documented on the Adverse Event CRFs.

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

Table 5 Guidance for Grading Adverse Events Not Evaluable under CTCAE V4.0

The Qualified Investigator, will evaluate all AEs according to:

V4.0 CTCAE Grading	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (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	An SAE is any AE occurring at any dose or during any use of Pembrolizumab 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 AE 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 an SAE.); 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 AE associated with an overdose is considered an SAE. An overdose that is not associated with an AE is considered a non-serious ECI 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 an SAE 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 AE. If less than 1 day, indicate the appropriate length of time and units.	
Action taken	Did the AE cause Pembrolizumab to be discontinued?	
Relationship to Pembrolizumab	Did Pembrolizumab cause the AE? The determination of the likelihood that Pembrolizumab caused the AE 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 AE based upon the available information. The following components are to be used to assess the relationship between Pembrolizumab and the AE ; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Pembrolizumab caused the AE:	
	Exposure	Is there evidence that the subject was actually exposed to Pembrolizumab 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 Pembrolizumab? 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 Pembrolizumab (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was Pembrolizumab 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 Pembrolizumab; or (3) the trial is a single-dose drug trial); or (4) Pembrolizumab is only used one time.)
	Rechallenge	Was the subject re-exposed to Pembrolizumab 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) Pembrolizumab is used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY PEMBROLIZUMAB, OR IF REEXPOSURE TO PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR 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 Pembrolizumab or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the CRFs /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 Pembrolizumab relationship).	
Yes, there is a reasonable possibility of Pembrolizumab relationship.	There is evidence of exposure to Pembrolizumab. The temporal sequence of the AE onset relative to the administration of Pembrolizumab is reasonable. The AE is more likely explained by Pembrolizumab than by another cause.	
No, there is not a reasonable possibility Pembrolizumab relationship	Subject did not receive Pembrolizumab OR temporal sequence of the AE onset relative to administration of Pembrolizumab is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

8.2.3 Sponsor Responsibility for Reporting Adverse Events

All AEs will be reported to regulatory authorities, REBs and Investigators in accordance with all applicable local and Health Canada regulations.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

ORR is the primary endpoint. Simon's two-stage design will be used. The null hypothesis that the true response rate is 20% will be tested against a one-sided alternative. In the first stage, 12 patients will be accrued. If there are 2 or fewer responses in these 12 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 25. The null hypothesis will be rejected if 8 or more responses are observed in 25 patients. This design yields a type I error rate of 0.1 and power of 0.8 when the true response rate is 40%.

9.2 Statistical Analysis Plan

The Kaplan-Meier method will be used to estimate the OS and PFS curve in the treatment group. Median OS and PFS and its 95% confidence interval in the treatment group will be estimated and reported.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 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 6.

Table 6 Product Descriptions

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

10.2 Packaging and Labeling Information

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

10.3 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.

10.4 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.

10.5 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.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor and any third parties (e.g. Merck or Qualtek).

Subjects are to be identified by a unique subject identification number. This number is assigned by the Sponsor at the time of registration.

Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

On the CRF demographics page, include the subject's age and date of birth.

For SAEs reported to the Sponsor, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

Documents that are not submitted to the Sponsor (e.g. signed informed consent forms) are to be kept in confidence by the Investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the REB direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study related records, including personal information.

11.2 Compliance with Law, Audit and Debarment

Audits and/or inspections may be made by the REB to ensure that the study has been conducted in accordance with the protocol, Health Canada regulations, and ICH/GCP. Audits and/or inspections may also be performed by Health Canada and the following entities:

- Alberta Health Services
- Audit/Regulatory at Merck Canada
- Regulatory/Audit Team at Tom Baker Cancer Centre

Monitoring for this study will be conducted on site and centrally as outlined in the monitoring plan. De-identified source data must be submitted to the Sponsor for the purposes of central

monitoring. Monitoring will occur over the course of the study to ensure data integrity and patient safety.

11.3 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.

11.4 Data Management

All trial data will be captured in the CRF within 20 business days after each treatment visit and 20 business days for subjects who are completing an off study visit.

Note that in the screening phase the Eligibility Screening Checklist must be submitted to and approved by the Sponsor prior to enrolling a subject on the study.

The site will be responsible for maintaining all trial related documentation for a period of 25 years as per the Health Canada retention requirements.

11.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) will be specific to this study and will be composed of independent medical reviewers. The members of the committee will be identified by the Sponsor and will be completely independent of the trial being monitored. The purpose of the DSMC is to advise on safety data, lack of efficacy and any other considerations within the charge of the Committee. Appropriate data summaries will be provided to the DSMC at the time of the analysis in regards to both safety and efficacy. The first DSMC meeting will occur after the 12th patient on treatment has either completed the Week 27 CT or MRI scans or has progressed or otherwise stopped study treatment and results have been received. The DSMC may be convened at any time to evaluate patient safety and trial efficacy concerns upon discretion of the Sponsor or DSMC. The DSMC will communicate to the Sponsor if the trial is to continue, be modified, or stopped as a result of the DSMC review.

12.0 APPENDICES

12.1 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.: <i>Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol</i> 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

The descriptions and grading scales found in the revised NCI CTCAE Version 4.0 will be utilized for AE reporting. (<http://ctep.cancer.gov/reporting/ctc.html>)

12.3 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.

12.4 Cockcroft and Gault Formula

Males

Creatinine clearance (mL/min) = $\{[140 - \text{age (years)}] \times \text{weight (kgs)} \times 1.23\} / \text{Serum creatinine (umol/L)}$

Females

Creatinine clearance (mL/min) = $\{[140 - \text{age (years)}] \times \text{weight (kgs)} \times 1.05\} / \text{Serum creatinine (umol/L)}$

12.5 References

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