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IND227: A Phase II/III Randomized Study of Pembrolizumab in Patients with Advanced Malignant Pleural Mesothelioma
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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II/III RANDOMIZED STUDY OF PEMBROLIZUMAB IN PATIENTS WITH ADVANCED MALIGNANT PLEURAL MESOTHELIOMA

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This study is a collaboration between CCTG, NCIN and IFCT.

(For contact information of study personnel see Final Page.)

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to Canadian Cancer Trials Group (CCTG). I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor. I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to CCTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified Investigator
(Printed name and signature)

Date

Protocol Number: CCTG IND.227

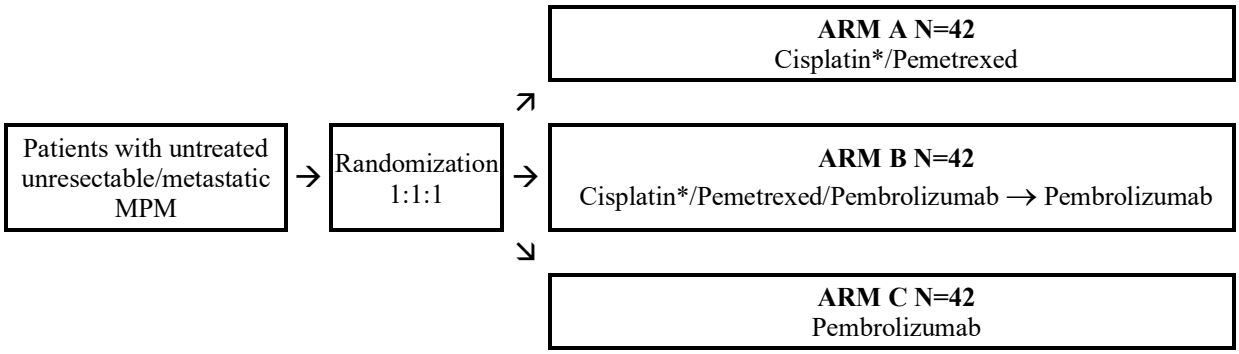
CENTRE: _____

TREATMENT SCHEMA

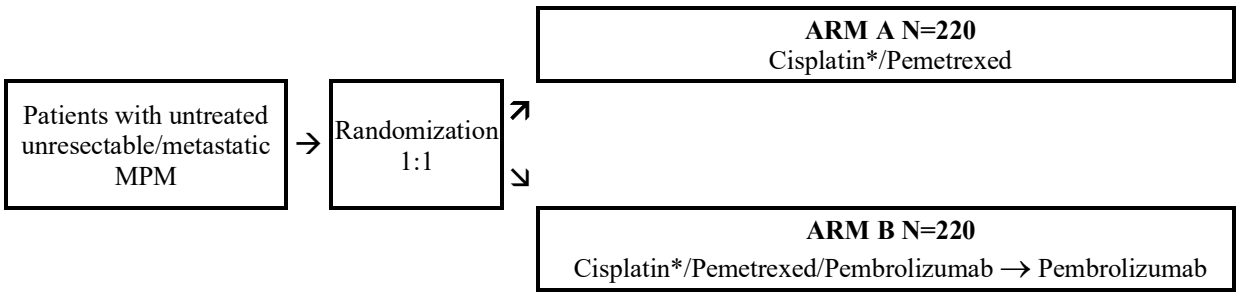
This is an academic open-label, multicentre, phase II/III randomized study in patients with malignant pleural mesothelioma (MPM) receiving first-line treatment for incurable advanced or metastatic disease. Patients will initially be randomized to one of 3 arms in 1:1:1 ratio, and then into one of 2 arms in a 1:1 ratio (phase II part 2 and phase III).

Patients will be stratified by histological subtype (epithelioid vs. other histology).

Phase II Schema:



Phase II/III Schema:



* carboplatin is acceptable after CCTG approval

1.0 OBJECTIVES

1.1 Primary Objective

Phase II:

- To evaluate whether pembrolizumab, alone or given to patients receiving standard chemotherapy, improves progression-free survival (modified RECIST 1.1 for mesothelioma (mRECIST)) in malignant pleural mesothelioma (MPM) compared to standard chemotherapy.

Phase III:

- To evaluate whether pembrolizumab improves overall survival when added to standard chemotherapy in malignant pleural mesothelioma (MPM).

1.2 Secondary Objectives

Phase II/III:

- To evaluate the tolerability of pembrolizumab, alone or given to patients receiving standard chemotherapy.
- To assess antitumour activity of pembrolizumab, alone or given to patients receiving standard chemotherapy including objective response rate (complete and partial response), using mRECIST.
- To evaluate the quality of life impact of pembrolizumab, alone or given to patients receiving standard chemotherapy as measured by time from randomization to first deterioration in the three common MPM Quality of Life scales.
- To evaluate whether pembrolizumab improves progression-free survival (mRECIST) when added to standard chemotherapy in malignant pleural mesothelioma (MPM).

Phase III:

- To evaluate the incremental cost effectiveness and cost utility ratios between arms.

1.3 Exploratory Objectives

- To explore the predictive and prognostic value of PD-L1 expression and presence of inflammatory cell subsets within the tumour microenvironment.
- To explore the predictive and prognostic value of exploratory blood-based biomarkers and genomic biomarkers.
- To evaluate the quality of life impact of pembrolizumab, alone or given to patients receiving standard chemotherapy as measured by standard QoL analyses.
- To assess antitumour activity of pembrolizumab, alone or given to patients receiving standard chemotherapy including immune (i) response rate (i-complete and i-partial response) using iRECIST modified for mesothelioma.

2.0 BACKGROUND INFORMATION AND RATIONALE

Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is a rare malignancy, with over 500 new cases diagnosed annually in Canada, *[Canadian Cancer Statistics Report, 2015]* and 3400 in the United States *[Price 2009]*. It is commonly associated with asbestos exposure. The incidence rates of mesothelioma are highest in Australia, Belgium and the United Kingdom, estimated at 30 cases per million *[Bianchi 2007]*. Due to the long latency period from initial exposure to asbestos and the presentation of MPM and continued use of asbestos in developing countries, the incidence of MPM will continue to rise around the world *[Robinson 2005; Stayner 2013]*.

Current Treatment Option and Outcome of Malignant Pleural Mesothelioma

Patients who present with localized disease (stage I and some stage II) MPM, young age, good cardiac and respiratory function, good performance status and epithelioid subtype may be candidates for multimodality therapy with extrapleuropneumectomy, hemithoracic radiation and/or neoadjuvant chemotherapy *[Sugarbaker 1999; Neragi-Miandoab 2008; de Perrott 2009; Cho 2014]*. Improved survival and possible cure were observed in this highly selected MPM patient population at the expense of toxicity.

However, the majority of MPM patients are not candidates for multimodality therapy and therapeutics options are palliative in nature. MPM patients with good performance status and organ function treated with the combination of cisplatin and an antifolate (pemetrexed or raltitrexed) derive less than 3 months of overall survival benefit (OS) over cisplatin alone, resulting in a median OS of approximately 1 year *[Vogelzang 2003; van Meerbeeck 2005]*.

High microvessel density, a marker for angiogenesis has been demonstrated in mesothelioma samples and was correlated with poor prognosis *[Ohta 1999]*. In addition, concurrent expression of VEGFR and VEGF in mesothelioma samples suggested the role of angiogenesis in the pathogenesis of mesothelioma *[Konig 1999; Strizzi L 2001]*. Bevacizumab as a single agent *[Jackman 2008]* and multi-targeted small molecules to VEGFR in both untreated and previously treated MPM showed at best modest clinical activity *[Papa 2013; Campbell 2012; Laurie 2011; Nowak 2012; Jahan 2012; Dubey 2010]*. Zalcman et al. reported a phase II/III trial of carefully selected patients with unresectable MPM treated with cisplatin/pemetrexed (up to 6 cycles) with or without bevacizumab at 15 mg/kg every 3 weeks (until progression or intolerable toxicity) *[Zalcman 2015]*. The bevacizumab-arm demonstrated a moderate improvement in median OS to 18.8 months from 16.1 months (HR=0.76, p=0.0127) and median progression-free survival (PFS) to 9.6 months from 7.5 months (HR=0.61, p<0.0001). The bevacizumab treated patients experienced statistically higher incidence of toxicity, particularly grade 3 or 4 hypertension, increase in creatinine, hemorrhage and arterial or venous thromboembolic events. Quality-of-life was similar between the two treatment arms. Patients with hemoglobin < 140 g/L, WBC ≥ 8.3 and poor prognosis (EORTC prognostic index *[Francart J 2009]*) did not appear to derive benefit from the combination (HR approximately 1). A trial comparing cisplatin/gemcitabine with or without bevacizumab in MPM patients failed to show any improvement in median OS, PFS or response rate *[Kindler 2012]*; second-line pemetrexed was used in this trial. A single arm phase II study of carboplatin/pemetrexed in combination with bevacizumab at 15 mg/kg every 3 weeks demonstrated a median PFS of 6.9 months and median OS of 15.3 months, failing to meet its primary endpoint of demonstrating an improvement in median PFS from 6 to 9 months *[Ceresoli 2013]*.
Currently bevacizumab is not considered standard of care, is not approved by Health Canada, and is not funded in Canada, Italy, France or other countries for MPM.

Immune System as a Target for the Management of Malignant Pleural Mesothelioma

MPM appears to be an immunogenic malignancy. Tumour infiltrating lymphocytes (TILs) in MPM tumour samples were first demonstrated to correlate with improved OS *[Leigh 1982]*. The presence of CD8+ T-cells in tumour samples from extrapleural pneumonectomy was associated with an improvement in OS, PFS and the absence of mediastinal nodal disease *[Anraku 2008; Yamada 2010]*, while the presence of CD4+, CD25+ or CD45RO+ T cells were associated with poorer OS. FOXP3+ on CD8+ T-cells, a marker for suppression of CD8+ T-cells, was not prognostic *[Anraku 2008]*. Mudhar et al. was not able to demonstrate prognostic significance of CD3 (pan-T-cell marker), CD45 (leukocyte common antigen), CD 20 (B-cell marker) and CD56 (NK cell marker), in 15 MPM samples *[Mudhar 2002]*.

In addition, there have been reports of spontaneous regression in MPM and long-term survival *[Robinson 2001; Pilling 2007; Allen 2007]*. Sterman et al. instilled single, escalating dose of IFN-beta gene containing adenovirus vector into the pleural cavity in 7 MPM patients and 3 patients with malignant pleural effusion. Seven out of 10 patients demonstrated INF-beta gene transfer and immune system activation. Four patients had FDG-PET changes suggesting benefit *[Sterman 2010]*.

PD-L1/2 and PD-1 and Cancer

Like any biological system, an activated immune system is tightly controlled to maintain homeostasis and thus prevent the occurrence of autoimmunity. Activation of the immune system by cancer cells is mediated through the activation of cytotoxic T-cells. These activated T-cells then migrate to the peripheral tissue to exert their anti-tumour effect. In the peripheral tissues, the interaction of PD-L1 and PD-L2 with PD-1 on cytotoxic T-cells negatively regulates these T-cells. This pathway has been extensively reviewed *[Yao 2013; Chen 2013; Naidoo 2014]*.

PD-L1 is expressed in tumour cells as well as other immune cells, including regulatory T-cells, B-cell, myeloid derived suppressor cells, natural killer (NK) cells, antigen presenting cells (APC) as well as vascular endothelial cells, whereas the expression of PD-L2 is more limited to APC in the lymphoid tissue or lymphoid organs, mast cells and selected tumour types including pancreas, ovarian and esophagus *[Zou 2008; Lee 2008; Leffers 2009; Hiraoka 2010; Nishimura 2000]*. PD-L1 is thought to dampen unwarranted T-cell function in the peripheral tissues and PD-L2 is thought to control T-cell activation in the lymphoid organs *[Lee 2008]*.

PD-L1 expression on tumour cells has been found to be associated with poor prognosis in a number of solid tumours. Kindler et al. reported 27% of MPM expressed PD-L1 either in the stromal cells or the tumour cells *[Kindler 2014]*. Two retrospective series *[Mansfield 2014; Cedrés 2015]* studied the relationship of PD-L1 expression and prognosis in MPM using 2 different immunohistochemistry antibodies (5H1-A3 and E1L3N) and cutoffs for PD-L1 positivity ($\geq$ 5% and >1%), respectively. PD-L1 was expressed in 20-40% of MPM and was more common in patients with non-epithelioid subtypes and was associated with significantly poorer prognosis (median OS 5 months versus not reached, $p<0.0001$ and 4.8 versus 16.3 months, $p=0.012$, respectively).

Pembrolizumab is an IgG4 kappa isotype antibody with stabilizing sequence alteration at the Fc domain to eliminate antibody directed cytotoxicity, targeting PD-1. Pembrolizumab has activity in a number of tumour types *[Hamid 2013; Robert 2014; Garon 2015; Patnaik 2015; Robert 2015]*.

Alley et al. reported the preliminary result of pembrolizumab at 10 mg/kg every 3 weeks in previously treated MPM patients in a phase Ib study. The overall response rate was 28% with stable disease in 48% of patients. Sixty-one percent of MPM had some reduction in the tumour size. The median PFS and duration of response were 5.8 months and not yet been reached (range 10-40+ weeks), respectively. Durable responses were observed in epithelioid and sarcomatoid subtypes of MPM, the latter is often considered as less chemotherapy sensitive. There was no correlation between PD-L1 expression and response to pembrolizumab *[Alley 2015]*.

Given the single agent activity of pembrolizumab, we plan to conduct a multi-centre, randomized phase II study of pembrolizumab given alone or with standard chemotherapy vs. standard chemotherapy alone in patients with malignant pleural mesothelioma.

Quality of Life

Assessment of quality of life (QoL) in all patients is an important aspect in this trial evaluating a new therapy given to patients with MPM. Any possible survival gains from new therapies need to be assessed in terms of their QoL impact. Patients on the standard regimen of cisplatin/pemetrexed are expected to see changes in self-reported QoL parameters reflecting an improvement in disease-related symptoms and temporary adverse effects specific to the chemotherapy, while overall QoL is maintained *[Arnold 2015]*. Those on cisplatin/pemetrexed plus pembrolizumab may see improvements in QoL if the combination is more effective, with the addition of specific adverse effects from the immune checkpoint inhibitor that may be highlighted in the pembrolizumab alone arm. However, it is possible that the pembrolizumab alone may be as effective as the cisplatin/pemetrexed with fewer adverse treatment effects. A patient perspective of the impact of treatment is felt to be an important part of this study.

Health Economics

The adoption and governmental/third party payer funding of new cancer therapeutics is dependent on the demonstration of cost effectiveness. Therefore, accurate prospective economic data for any new therapeutic is critical to assist decision makers regarding funding issues.

A prospective economic evaluation will be conducted to determine the incremental cost-effectiveness and cost-utility of adding immunotherapy to standard platinum combination chemotherapy from a government payer perspective, by prospectively collecting economic and resource utilization information during the phase III portion of the trial. As part of the economic evaluation in this study, patient preferences, or utilities, will be measured using the EQ-5D questionnaire *[Brooks 1996]*. The EQ- 5D self-administered questionnaire consists of two pages comprising the EQ-5D descriptive system and the EQ Visual Analogue Scale (VAS). The EQ-5D descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension comprises five levels (no problems, slight problems, moderate problems, several problems and extreme problems). A unique EQ-5D health state is defined by combining one level from each of the five dimensions. The VAS records the respondent's self-rated health status on a vertical graduated (0-100) visual analogue scale. The EQ-5D is a validated instrument that has been used in population surveys and clinical trial settings. Analysis will be performed as detailed in the statistical section of the protocol (see Section 13).

3.0 BACKGROUND THERAPEUTIC INFORMATION

Please consult the current pembrolizumab Investigator Brochure (IB) for additional details and the most up-to-date information.

3.1 Pembrolizumab

3.1.1 *Name and Chemical Information*

Pembrolizumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2).

3.1.2 *Chemical Structure*

Pembrolizumab is an IgG4/kappa immunoglobulin with a stabilizing S228P sequence alteration in the fragment crystallizable (Fc) region. The antibody is heterogeneously glycosylated at asparagine 297 within the Fc domain of each heavy chain, yielding molecular weights typically ranging between 148.9 and 149.5 KDa, depending on the attached glycan chains.

3.1.3 *Mechanism of Action*

Pembrolizumab with high affinity and specificity binds to human PD-1 and blocks the interaction between PD-1 and its ligands: PD-L1 and PD-L2. In vitro studies, pembrolizumab strongly enhances T-lymphocyte immune responses by modulation of interleukin-2 (IL-2), tumour necrosis factor alpha (TNFα) and interferon gamma (IFNγ) levels. Pembrolizumab potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T-cells. Pembrolizumab does not induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

3.1.4 *Clinical Trials*

The profile of adverse events (AEs) and the spectrum of AE severity are similar across trials in both monotherapy and combination trials. The most common treatment related adverse events (all grades) were nausea, fatigue, diarrhea, cough, neutropenia, thrombocytopenia, anemia, decreased appetite, pruritus, rash, constipation, dysphonia, arthralgia, headache, vomiting, asthenia, pyrexia, back and abdominal pain, and increased AST and ALT. Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving pembrolizumab, including Grade 2 (6.2%) and Grade 3 (0.1%) hypothyroidism.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, thyroid disorders (hypothyroidism and hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, and nephritis. After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction; these are included in the reference safety information below. The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

3.1.5 *Pharmaceutical Data*

Supplied:
Pembrolizumab is provided as a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vials containing 100 mg/4 mL of pembrolizumab.

It is formulated with L-histidine as a buffering agent, polysorbate 80 as a surfactant and sucrose as a stabilizer/tonicity modifier and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (if necessary).

Stability:
The shelf life of pembrolizumab will be indicated on the vial label.

Storage:
Pembrolizumab must be stored at 2°C to 8°C.

Route of Administration:
The route of administration for pembrolizumab is intravenous.

If needed pembrolizumab can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of 4 hours. This includes both the admixture solutions in IV bags and the duration of the infusion. Additionally IV bags can be stored at 2°C to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted pembrolizumab solutions in the IV bags.

The solution should be administered intravenously over 30 minutes using a sterile, non-pyrogenic low-protein binding 0.2 to 5 μm in-line or add-on filter.

3.1.6 *Rationale for Flat Dosing of Pembrolizumab*

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). This dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W);
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and;
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumour (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumour types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumour type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumour PD-1 saturation over a wide range of tumour penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumour.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected.

3.2 Cisplatin (and Carboplatin *if used*)

Cisplatin and carboplatin are commercially available and approved for the treatment of patients with mesothelioma. This drug will not be supplied but should be dispensed from the centre's pharmacy supply. Refer to package insert, product monographs and provincial formularies for further information.

3.3 Pemetrexed

Pemetrexed is commercially available and approved for the treatment of patients with mesothelioma. This drug will not be supplied but should be dispensed from the centre's pharmacy supply. Refer to package insert, product monographs and provincial formularies for further information.

4.0 STUDY POPULATION

This study is designed to include women and minorities, but is not designed to measure differences in intervention effects.

4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed prior to randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

4.1.1 Patients must have histologically confirmed malignant pleural mesothelioma. Patients must be eligible to receive standard chemotherapy with pemetrexed and cisplatin and have no contraindications to standard chemotherapy.

4.1.2 Patients must have unresectable advanced and/or metastatic disease, incurable by standard therapies.

4.1.3 All patients must have a cellular tumour block from their primary or metastatic tumour available and consent to release the block/recently cut slides for correlative analyses (See Section 11.0) and the centre/pathologist must have agreed to the submission of the specimen(s).

4.1.4 Presence of radiologically documented disease. At least one site of disease must be unidimensionally measurable* by mRECIST or RECIST 1.1 (see Section 8.0) as follows:

CT scan (with slice thickness of ≤ 5 mm)	≥ 10 mm →	longest diameter
Physical exam (using calipers)	≥ 10 mm	
Lymph nodes by CT scan	≥ 15 mm →	measured in short axis

Pleural rind as defined by Byrne et al *[Byrne 2004]*.

* *Consult CCTG if the patient does not have a measurable pleural rind; if RECIST 1.1 is used rather than mRECIST pleura is considered a non-target lesion and the patient may not be eligible.*

All radiology studies must be performed within 21 days prior to registration (exception: within 28 days if negative).

4.1.5 Age ≥ 18 years.

4.1.6 ECOG performance status 0 or 1.

4.1.7 *Previous Therapy*

Cytotoxic Chemotherapy:

- Patients must not have received prior chemotherapy for any stage of advanced/metastatic disease.
- Patients who received previous (neo)adjuvant cisplatin-based systemic chemotherapy must have received the last dose of chemotherapy at least 12 months before registration. Please contact CCTG PRIOR to randomization for such patients.

Other Anti-Cancer Therapy:

- Patients may not have received targeted small molecule therapy, immunotherapies and viral therapies, biologic therapies and angiogenesis inhibitors for advanced/metastatic disease, or any prior immunotherapy for any stage of disease.

Radiation:
Patients may have had prior radiation therapy, but NOT to the thorax unless clear disease progression has been demonstrated and confirmed with CCTG. A minimum of 28 days must have elapsed between the end of radiotherapy and registration onto the study. Radiation must have involved < 30% of functioning bone marrow and there must be measurable disease outside the previously irradiated area (patients whose sole site of disease (for example pleural rind) is in a previously irradiated area are ineligible UNLESS there is evidence of progression, or new lesions have been documented, in the irradiated field). Please contact CCTG PRIOR to randomization if the patient has received prior thoracic radiation. Patients must have recovered from any acute toxic effects from radiation prior to registration.

Previous Surgery:
Previous major surgery is permitted provided that it has been at least 28 days prior to patient registration and that wound healing has occurred.

4.1.8 Laboratory Requirements (must be done within 7 days prior to registration).

Hematology	Absolute neutrophils	$\geq 1.5 \times 10^9$/L
	Platelets	$\geq 100 \times 10^9$/L
	Hemoglobin	≥ 90 g/L*
Chemistry	Bilirubin	≤ 1.5 x ULN (upper limit of normal)**
	AST and ALT	≤ 2.5 x ULN
	Serum creatinine *or:* Creatinine clearance***	< 1.25 x ULN ≥ 50 mL/min

* Contact CCTG if patient is not decompensated, is asymptomatic and transfusion is not indicated.
** If confirmed Gilbert's, eligible providing ≤ 3 x ULN.
*** Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft and Gault equation below:

$$\text{Females: GFR} = \frac{1.04 \times (140 - \text{age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$$

$$\text{Males: GFR} = \frac{1.23 \times (140 - \text{age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$$

4.1.9 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to registration in the trial to document their willingness to participate. Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

4.1.10 Patients must be accessible for treatment, response assessment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Patients must agree to return to the participating centre for management of any adverse events which may occur through the course of the trial. This implies there must be reasonable geographical limits placed on patients being considered for this trial. Sites are encouraged to contact CCTG (or their respective Cooperative Group for sites outside Canada) for any questions regarding the interpretation of this criterion. Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

4.1.11 In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient randomization.

4.1.12 Women/men of childbearing potential must have agreed to use two highly effective contraceptive methods during the study and for six months after discontinuation. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin (β-HCG) is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patient will be considered eligible if an ultrasound is negative for pregnancy.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4.1.13 Patient must be able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires. The baseline assessment must already have been completed. Inability (illiteracy, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

4.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (at doses more than 10 mg prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first and any dose of trial treatment.

4.2.2 Has active autoimmune disease that has required systemic treatment in the past 3 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs) or history of allogeneic transplantation. 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.

4.2.3 Must not have received a live vaccine within 30 days of planned start of study therapy.

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

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

4.2.5 Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (including cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects) or who have had unstable angina congestive heart failure or myocardial infarction within the previous year. Patients with a significant cardiac history, this includes hypertension, even if controlled, should have a LVEF $\geq$ 50%.

4.2.6 Patients with a history of other malignancies unless having undergone curative therapy (i.e. resection, radiation, etc.) and do not require concurrent anticancer therapy.

4.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab or any of the other chemotherapy agents.

4.2.8 Concurrent treatment with other investigational drugs or anti-cancer therapy.

4.2.9 Patients with serious illness or medical condition that would not permit the patient to be managed according to the protocol including, but not limited to:

- History of significant neurologic or psychiatric disorder which would impair the ability to obtain consent or limit compliance with study requirements.
- Active infection requiring systemic therapy; (including any patient known to have active hepatitis B, hepatitis C or human immunodeficiency virus (HIV) [note: testing in asymptomatic patients is not required] or tuberculosis).

- Known history of, or any evidence of active, non-infectious pneumonitis.
- Any other medical conditions that might be aggravated by treatment.
- Serious or non-healing wound, ulcer, or bone fracture.

4.2.10 Patients with evidence of interstitial lung disease.

4.2.11 Patients with severe/ uncontrollable tumor pain that requires radiation prior to starting on systemic therapy.

4.2.12 Pregnant or lactating women. (N.B.: All women of childbearing potential must have a negative pregnancy test within 72 hours prior to registration).

5.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

Required Investigations	Pre-study (≤ 7 days prior to registration)	Day 8 for cycle 1 only	Day 1 each cycle, and as clinically indicated	Every 6 weeks for 3 assessments then every 12 weeks	4 weeks after completion of all protocol therapy	Post-treatment: Every 12 weeks until confirmed PD, then every 24 weeks until death [1]
History and Physical Exam						
Including: height and weight, ECOG performance status, documentation of all measurable and non-measurable disease, clinical tumour measurements (if applicable); Vital signs: blood pressure, heart rate, temperature	X		X		X	
Laboratory Procedures/Assessments*						
CBC, neutrophils, lymphocytes, platelets	X	X[2]	X		X[3]	X[3]
PTT, PT/INR (only for patients on anticoagulants)	X	X[15]	X[15]		X[15]	X[15]
Serum creatinine, (calculated creatinine clearance as required), bilirubin, ALP, AST, ALT, LDH, albumin, glucose, amylase[4], lipase[4], TSH[5], CRP	X[16]	X[2]	X		X[3]	X[3]
Pregnancy Test[6]	X		X[7]			
Urinalysis	X[15]		X[15]			
Radiology						
Tumour Imaging (Chest/upper abdomen CT scan; other scans as necessary to document disease)	X[8]			X[8]	X[9]	X[9]
Quality of Life[10]						
EORTC QLQ-C30 & QLQ-LC13	X		X		X	X[10]
Health Economics (Phase III)						
Heath Utilities Index (EQ-5D 5L)	X		X		X[11]	X[11]
Other Investigations						
EKG	X[15]		X[15]			
LVEF	X[12]					
Archival Tumour Tissue	X[13]					
Correlative Studies Blood Collection (plasma and serum)	X[14]	See Section 11.0 for details				
Adverse events	X	Continuously			X[1]	

footnotes on next page …

*	Pre-treatment blood draws and physical exams may be done two working day prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
1	Patients must be followed for 90 days after last dose of protocol therapy for any SAE or Event of Clinical Interest (See Section 9.0). Thereafter, only SAEs related to protocol therapy are reported. Other adverse events felt to be related to protocol therapy will be followed until resolved to ≤ Grade 2. Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) (see Appendix IV).
2	Only for first 12 pts in each arm (no longer applicable as of May 15, 2017).
3	Required at 4 weeks. To be done additionally every 3 months thereafter to follow abnormal lab results felt related until resolved to ≤ Grade 2.
4	It is preferable that both amylase and lipase are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.
5	TSH to be done at baseline and every six weeks; If abnormal, T3 and T4 must be measured.
6	For women of childbearing potential only (urine or serum test). Within 72 hours prior to registration. Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.
7	As clinically indicated in WOCBP
8	To ensure comparability, baseline scans and subsequent scans to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Maintain schedule every 6 weeks even if cycles are delayed.
9	To be done additionally every three months thereafter until confirmed relapse or progression for patients with CR, PR, SD response. If iUPD occurs, confirmatory scans must be performed at least 4 weeks, but no longer than 8 weeks, after iUPD was identified.
10	Quality of Life Questionnaires will be completed at baseline, prior to each cycle, 4 weeks after completion of protocol therapy and at each follow-up visit. Short follow-up until confirmed progressive disease. Questionnaires to be completed up to and at time of confirmed progressive disease (if not done within 2 weeks prior to PD).
11.	The EQ-5D-5L will be completed at baseline, prior to each cycle, 4 weeks after completion of protocol therapy and at each follow up visit. Short follow up until confirmed progressive disease. Questionnaires to be completed up to and at time of confirmed progressive disease (if not done within 2 weeks prior to PD).
12	Only if significant cardiac history (see Section 4.2.5) and for patients who develop persistent, confirmed T wave repolarization abnormality (inversion or flattening) and then if abnormal EKG or LVEF on treatment and/or clinically indicated. At investigator's discretion for all other patients. Ejection fraction must be determined using the same technology used at baseline (ECHO or MUGA). Recommended within 7 days but up to 28 days permissible.
13	Must be confirmed available prior to registration on ALL patients. Archival tissue submission should be sent at the same time that the baseline CRF is submitted for each patient. See Section 11.0 for details.
14	After registration but before the first dose of study treatment.
15.	Only at baseline and thereafter as clinically indicated.
16.	Electrolytes only in phase II.

6.0 ENTRY/RANDOMIZATION PROCEDURES

6.1 Entry Procedures

All registrations and randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the IND.227 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing patients please contact the help desk (link in EDC) or the IND.227 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG IND.227)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values
- BSA, height and weight
- stratification factors

6.2 Stratification

Subjects will be stratified at the time of randomization by:

- Histological subtype:
  - epithelioid
  - other histological subtypes

6.3 Randomization

Randomization will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission (including the completion and submission of questionnaires such as QoL) cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required.

7.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient registration.

Pemetrexed and cisplatin will be administered after pembrolizumab at the doses specified below. A maximum of 6 cycles will be administered based on ASCO guidelines which recommend 4-6 cycles *[Kindler 2018]*.

Administration and hydration will be performed according to the product monograph as well as national, provincial and local guidelines. Patients must be informed of the need to discontinue non-steroidal anti-inflammatory drugs (NSAIDs) and other nephrotoxic drugs and be given standard vitamin supplementation.

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix IV). Investigators must consult the product monographs for each chemotherapy agent, or follow their local or provincial formulary guidelines for dose modifications.

Alternatively, standard protocols are available on the Cancer Care Ontario website: https://www.cancercare.on.ca/toolbox/drugformulary.

Patients should receive standard premedication according to the product monograph and local and provincial formulary guidelines:

- antiemetics
- hydration (for cisplatin)
- vitamin supplementation for pemetrexed (both starting ≥ 1 week prior to pemetrexed administration) continue throughout and 3 weeks after last dose of pemetrexed:
  - Vitamin B12 (1000 mcg IM every 9 weeks);
  - folic acid 0.4-1 mg PO OD
- steroid prophylaxis (for pemetrexed):
  - dexamethasone 4 mg PO BID for 3 days starting day before chemotherapy suggested for rash prophylaxis

Note: The use of steroids for the prevention and treatment of emesis should be minimized where feasible and other effective anti-emetics used where possible. If emesis is well controlled, investigators should consider reducing or discontinuing steroids (above that given for rash prophylaxis) for subsequent cycles.

Note: **Contact CCTG if cisplatin is contraindicated**. The substitution of carboplatin (AUC 5-6) for cisplatin is permitted on a case-by-case basis but only after review and approval by CCTG.

Note: For pembrolizumab sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes: -5 min/+10 min).

Arm A

Agent(s)	Dose	Route	Schedule
Pemetrexed	500 mg/m^2	IV	Day 1 every 21 days for 6 cycles
Cisplatin	75 mg/m^2	IV	Day 1 every 21 days for 6 cycles

Arm B

Agent(s)	Dose	Route	Schedule
Pembrolizumab	200 mg*	IV	Day 1 over 30 min every 21 days for a total of 2 years
Pemetrexed	500 mg/m^2	IV	Day 1 every 21 days for 6 cycles
Cisplatin	75 mg/m^2	IV	Day 1 every 21 days for 6 cycles
* Patients who have discontinued pembrolizumab for toxicity may NOT restart pembrolizumab even after they complete standard chemotherapy.			

Arm C (Phase II only)

Agent	Dose	Route	Duration	Schedule
Pembrolizumab	200 mg*	IV	30 min	Day 1 every 21 days for a total of 2 years
* Patients who have discontinued pembrolizumab for toxicity may NOT restart pembrolizumab.				

7.1 Premedication

For patients receiving pembrolizumab the use of premedication (e.g. for nausea) or hypersensitivity prophylaxis is not required. Management of symptoms should take place as necessary (see Section 7.3 below). See Section 7.3.1 with respect to premedication of patients that have had a prior ≤ Grade 2 infusion-related reaction. Details of any premedication or concomitant medication given to manage or prevent adverse events should be recorded on the electronic case report form (eCRF).

7.2 Patient Monitoring

Patients will be monitored during the infusion and after the infusion with assessment of vital signs as per local procedures. A 1-hour observation period is recommended after the first infusion of pembrolizumab-containing regimen. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each pembrolizumab-containing regimen infusion).

Guidelines for management of infusion-related reaction are summarized in Section 7.3.1.

All patients should be closely monitored according to guidelines in Section 7.3 and be advised to contact the treating centre in the case of significant toxicities.

7.3 Dose Interruptions and Management of Toxicity

The major toxic effects of pembrolizumab that are anticipated to limit dosing are hypersensitivity/infusion related reactions and possible class related immune related AEs (irAEs), based on the mechanism of action of pembrolizumab leading to T-cell activation and proliferation. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Potential immune related AEs include pneumonitis, colitis, thyroid disorders (hypothyroidism/hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, nephritis, pancreatitis, myositis, myocarditis, sarcoidosis, encephalitis and severe skin reaction (dermatitis). Mild irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as tumour necrosis factor blockers), when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants. See Section 7.3.2 for supportive care guidelines, including use of corticosteroids.

If an irAE is suspected, a thorough evaluation should be conducted in an effort to possibly rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity.

The next cycle should not be given until the laboratory criteria in Section 4.1.8 are met and resolution of all clinically significant drug related toxicity to ≤ grade 2 and steroids, if used, have been tapered to ≤ 10 mg prednisone equivalents per day. For patients continuing on pembrolizumab alone, dosing may be based on requirements of the current product monograph (for example for renal function) for pembrolizumab but must be discussed with CCTG.

The guidelines that follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that requires the greatest dose hold or discontinuation. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix IV).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

The following general guidance should be followed for management of toxicities:

1. Treat each of the toxicities with maximum supportive care (including slowing / interrupting / omitting the agent suspected of causing the toxicity where required).
2. If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of pembrolizumab along with appropriate continuing supportive care.

In addition to the dose adjustments shown in this section, the following are recommended:

- Patient evaluation to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.

- Symptomatic and topical therapy should be considered for low-grade events.
- For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone PO 1-2 mg/kg/day or IV equivalent.
- If symptoms recur or worsen during corticosteroid tapering (> 4 weeks of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4 mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate.
- More potent immunosuppressive drug (refer to individual sections of the immune related adverse event for specific type of immunosuppressive drugs) should be considered for events not responding to systemic steroids.
- Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient and be discussed with CCTG.

7.3.1 *Infusion Reactions*

Study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to appropriate drugs and medical equipment to treat acute anaphylactic reactions, emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary. Table 1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 1: Treatment Guidelines for Treatment of Infusion Reaction Associated With Administration of Pembrolizumab.

Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion**. 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Participant 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 analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

7.3.2 *Immune Related Adverse Events*

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and summarized in Table 2.

The next cycle should not be given until the laboratory criteria in Section 4.1.8 are met and resolution of all drug related toxicity to ≤ grade 2 and steroids, if used, have been tapered to ≤ 10 mg prednisone equivalents per day. Discuss with CCTG if clarification is required.

Table 2: Dose Modification Guidelines for Drug-Related Adverse Events

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
			•	•

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

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

If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 7.3.2 for dose modification. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

7.3.3 *Other (Non-Immune Related) Adverse Events Related to Study Therapy*

CTCAE Grade	Dose Adjustment
Grade 1	• None
Grade 2 *	• If clinically significant, hold/omit until resolution to ≤ Grade 1 or baseline and next planned infusion.
Grade 3	• Hold/omit until resolution to ≤ Grade 1 or baseline and next planned infusion. • For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume at next planned infusion. • Otherwise, discontinue
Grade 4	• Discontinue. (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with CCTG).
* Excluding: fatigue, alopecia; inadequately controlled/managed diarrhea, nausea or vomiting.	

7.4 Duration of Therapy

Treatment will continue until the criteria for removal from protocol treatment have been met (see Section 10.1).

7.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the CCTG Clinical Trial team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

7.5.1 *Permitted Concomitant Therapy*

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

Growth factors may be used according to centre policy but cannot be used in place of protocol defined dose adjustments or delays. Please consult CCTG in the case of patients experiencing multiple delays as exceptions may be made for patients who are benefitting from protocol therapy.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and Events of Clinical Interests as defined in Section 9.0.

7.5.2 *Not Permitted Concomitant Therapy*

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

- antineoplastic systemic chemotherapy or biological therapy,
- radiation therapy, patients who require radiation must receive this prior to entry, bearing in mind this may preclude participation (see Section 4.1.7 and 4.2.11). Patients who require radiation on study are considered to have disease progression (contact CCTG if clarification is required).
- live vaccines,
- systemic glucocorticoids other than specified in this protocol. Note: Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed, as are oral dose of steroids equivalent to 10 mg or less of prednisone.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.2 Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Seymour 2017]*.

Response and progression will be evaluated in this study using mRECIST, based on the revised international criteria (RECIST 1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as iRECIST guidelines *[Armato 2018; Seymour 2017]*. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

8.2 Response and Evaluation Endpoints

Response and progression on all arms of this study will be evaluated in this study using a modified RECIST (mRECIST) developed by Byrne and Nowak *[Armato 2018; Byrne 2004]* for assessment of response in malignant pleural mesothelioma. The modification is based on the international criteria proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee. In addition, as an exploratory endpoint, iRECIST will be used. Investigators should continue treatment, as appropriate, in the absence of unacceptable toxicity, until unequivocal disease progression. This is particularly important for patients in whom pseudoprogression may have occurred. Follow up response assessments must be continued until confirmed disease progression has occurred. See 8.2.1 for measurement of the pleural unidimensional measure.

Note: consult CCTG if the patient does not have measurable pleural rind; if RECIST 1.1 is used primarily, note that pleura is considered a non-target lesion and the patient may not be eligible.

8.2.1 *Pleural Tumour Measurement*

The pleural tumour thickness should be measured perpendicular to the chest wall or mediastinum. It should be measured in 2 positions at 3 different levels ('cuts') on the thoracic CT scan. The 'pleural unidimensional measure' is the sum of these 6 measurements. The transverse cuts should be at least 1 cm apart, and must lend themselves to repeated measures for ease of re-assessment, be related to anatomical landmarks in the thorax. Cuts should preferably superior to left atrium or below the aortic arch. At reassessment, the pleural thickness must be measured at the same level and position. Fissural disease can be measured, using perpendicular to a tangent to pleura, once measured at baseline it must be oriented in the same direction for all subsequent scans.

The pleural unidimensional measure is considered to be one organ (8.2.4) and only one value should be provided.

8.2.2 *Other Measurable Disease*

Other measurable tumour lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.3 *Non-Measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.4 *Target Lesions*

When more than one measurable tumour lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.2.5 *Non-Target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent". **Note: For this study, skin lesions will be considered as non-target lesions.**

8.2.6 *Response*

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

Complete Response (CR): disappearance of *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Eisenhauer 2009]*) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression.
See Section 8.3.

Table 3: Integration of Target, non-Target and New Lesions into Response Assessment:

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

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

* Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments

8.3 Immune-Related Response Assessment

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

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

Confirming Progression

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

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

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

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New Lesions

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

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of NLT should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

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

Table 4: Time-point (TP) iResponse

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

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

Table 5: iRECIST Best Overall Response (iBOR)

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomized study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

8.4 Response Duration (mRECIST and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

8.5 Stable Disease Duration

Stable disease duration will be measured from the time of start of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.6 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

8.6.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.6.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.6.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case *[Eisenhauer 2009]*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

8.6.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

8.6.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

8.6.6 *Tumour Markers*. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

8.6.7 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

9.0 SERIOUS ADVERSE EVENT REPORTING

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

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' or reportable Event of Clinical Interest (ECI) is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG. Any event which meet these criteria must be reported from the time the patient is registered/randomized. All registered/ randomized patients must be followed for SAEs or ECIs until 90 days after last dose of protocol therapy and thereafter any related SAE. See below for reporting requirements.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events irrespective of relation to pembrolizumab or standard chemotherapy must be reported in an expedited manner (see Section 9.3 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and for these events considered related to pembrolizumab or standard chemotherapy at any time afterwards.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect (see 9.3)
  - Pregnancy or exposure (pembrolizumab patients only see 9.3)
  - Diagnosis of a non MPM cancer
  - An overdose of pembrolizumab; defined as any dose of 1,000 mg or greater (≥ 5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with the overdose of pembrolizumab, the adverse event(s) is also reported as a serious adverse event.
  - An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

Lack of efficacy (i.e. disease progression) is not considered to be an adverse event.

9.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the IND.227 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.
Within 7 days:	Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

IND.227 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2411

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the IND.227 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

9.3 Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criteria 4.1.12. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.3.2 *Pregnancy and Lactation Reporting*

The investigator is required to report to CCTG any pregnancy and lactation occurring during the study in female participants, and female partners of male participants.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer 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 serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to CCTG.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization 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.

The investigator should report the pregnancy in a timely manner, within 1 working day of learning of the pregnancy without delay using the CCTG Pregnancy Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the CCTG. If the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) CCTG must be notified within 1 working day. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada and Other Regulatory Authorities Where the Trial is being Conducted

CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

CCTG will provide expedited reports of SAEs to the local sponsors for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out). NCIN is responsible for reporting relevant events to the European authorities (EudraVig).

9.5 CCTG Reporting Responsibility to Merck & Co., Inc.

Merck & Co., Inc. Global Safety will be notified of all protocol reportable serious adverse events, ECIs and pregnancy/lactation reports (as defined in Section 9.0) within one working day of receipt of report at CCTG. CCTG, as sponsor, will determine regulatory reportability.

9.6 Merck & Co., Inc. Reporting Responsibilities

Merck & Co., Inc. will report all pembrolizumab regulatory reportable serious adverse events from non-CCTG trials (Safety Updates) to Health Canada and other Regulatory Authorities (when applicable) and will also provide line listings of regulatory reportable safety updates to CCTG in the format and within the timelines specified in the contract.

9.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial IND.227 web-based safety monitoring utility.

Canadian Sites:
Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial IND.227 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

Non-Canadian Sites:
Investigators must notify their REB according to national and local policies. Additional reports may be required and will be provided by the local sponsor as appropriate.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness that would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Tumour progression or disease recurrence as defined in Section 8.0. Note: investigators may continue treatment in the face of equivocal disease progression (iUPD) until the next assessment (see Section 10.2).
- Request by the patient.
- Completion of therapy as outlined in Section 7.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Duration of Protocol Treatment

- Patients should continue standard chemotherapy for a maximum of 6 cycles in the absence of unacceptable toxicity. Contact CCTG if clarification is required.
- Patients should continue pembrolizumab (with or without standard chemotherapy) for a maximum of two years.
- Patients on pembrolizumab containing arms who progress with confirmed progression according to iRECIST will discontinue pembrolizumab as well as standard chemotherapy (if applicable) at the time progression is documented.
- Patients on non-pembrolizumab containing arms who progress with progression according to RECIST 1.1 will discontinue standard chemotherapy at the time progression is documented, however, centres are strongly encouraged to ‘confirm’ progression after at least 4 weeks providing that subsequent anticancer treatment has not been initiated at that time.

10.3 Therapy After Protocol Treatment is Stopped

Further treatment, if any is at the discretion of the investigator. No cross-over is planned.

10.4 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. Follow-up will be required every 3 months until relapse (see Section 5.0 for investigations to be performed) and every 6 months until death.

If patient is unable to return to participating centre for follow up, please contact CCTG to discuss possible options prior to considering ‘withdrawal of consent’ processes. Remote oversight allowing data submission may be feasible. Death Report will be required for all patients, due within 2 weeks of knowledge of death (see Appendix III - Documentation for Study).

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Data Review

CCTG receives core support from the Canadian Cancer Society. To ensure efficient use of limited funding, the CCTG has, over the past 40 years, optimized their risk based trial oversight and monitoring program. A critical component is central data review of submitted deidentified source documents, allowing source data verification and confirmation of key aspects including eligibility, endpoints and safety outcomes. Depending on the trial's design, these source documents may include such source documents as surgical and histopathology reports to confirm disease stage and type, imaging reports to confirm extent of disease and assess efficacy, or include submission of tumour samples (to confirm diagnosis and eligibility or DICOM images (to verify response or radiation therapy planning). These source documents are reviewed by experienced data managers and physicians and are critical to ensuring the accuracy of the data and consistency of conclusions drawn.

The collection of this critical data involves uploading documents through the password protected and secure CCTG electronic Supporting Document Upload Tool (SDUT) data capture linked system. See Appendix III (Documentation for Study) for details of supporting document requirements for this trial and for requirements for the redaction of personal identifiers. Although it remains the centres responsibility to ensure adequate redaction of any information provided to CCTG, submitted source documents are reviewed prior to acceptance at CCTG; in the case of incomplete redaction, documents are removed and the site assigned a violation and required to resubmit.

All patients will provide written informed consent for submission of source documents, and the rationale and documents to be collected will be detailed in the informed consent document.

11.2 Central Radiology Review

A central review of x-rays and/or scans is planned to confirm the date of progression. A blinded independent review (BICR) will be conducted. For purposes of reporting, the results of both local (investigator assessment of response) and BICR will be included. Sites must submit copies of all imaging (see Radiology Submission Manual).

11.3 Central Pathology Review

Central pathology review is planned for this study. Pathology review may be done for all patients to confirm the histology and subtype of the previously diagnosed pleural mesothelioma. Pathologist(s) will review digital images from the original HE slides but may require submission of additional sections for staining and evaluation. Results of the central pathology review will not be provided to the originating institution, nor included in the patient record.

11.4 Tissue Collection (Mandatory)

Archival Tumour Block/Slides:
The collection of a representative block of the diagnostic tumour tissue is an important part of this trial. Blocks or freshly cut slides will be sent to the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario. Tumour blocks will be the preferred material to collect, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

The tissue will be used by researchers to better understand the nature of malignant pleural mesothelioma and how patients respond to treatment by the tests described in the protocol. Samples will be used for research purposes in this protocol only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/ histology number and/or patient initials. Material issued to researchers to perform the protocol defined tests will be anonymized and only identified by a coded number.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen's Department of Pathology to pathology departments for a representative tumour block.

Genetic Testing

Planned testing for hereditary genetic defects predisposing to malignant disease will not be carried out. All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

Planned priority assays on tumour tissue include:

- PD1, PD-L1, PD-L2.
- Evaluation of lymphocyte, macrophage and other cellular infiltration including subtypes by immunohistochemistry (including TILs, CD8 and FOXP3).
- Genomic profiling.

11.5 Blood Collection

The CCTG is interested in exploring the use of surrogate tissues such as serum and plasma in evaluating potential prognostic or predictive biomarkers, or as evidence of pharmacodynamic effects. Blood, serum and plasma samples will be collected for planned studies from all patients. Samples will be used for research purposes in this protocol only and will not be sold.

Exploratory assays include:

- Mesothelin
- Genomic profiling
- HLA subtyping

Detailed instructions for sample acquisition, preparation, and shipping are found in the IND.227 lab manual.

12.0 STATISTICAL CONSIDERATIONS

12.1 Objectives and Design

The primary objective of this randomized phase II/III trial is to evaluate whether pembrolizumab, single agent or added to standard chemotherapy, improves overall survival (OS) in malignant pleural mesothelioma. Secondary objectives include evaluation of the safety and tolerability, progression free survival (PFS), objective response rate (ORR; using modified RECIST 1.1 for mesothelioma (mRECIST) for both PFS and ORR), quality of life, and health economic evaluation. Exploratory objectives include evaluating predictive and prognostic value of exploratory blood-based biomarkers, additional QoL analyses, and evaluating efficacy using iRECIST.

A randomized phase II study with progression free survival as the primary endpoint was planned be conducted first randomizing patients in 1:1:1 ratio by a minimization algorithm into the following three arms: cisplatin/pemetrexed (Arm A), cisplatin/pemetrexed/pembrolizumab (Arm B), pembrolizumab (Arm C) after stratification by histological subtype (epithelioid vs. other).

A full safety review by the trial committee was performed when 12 patients have been randomized to each arm and followed for at least 6 weeks to ensure the tolerability and safety of combining pembrolizumab with chemotherapy.

A phase II interim analysis based on 16 week disease control rate (DCR) was performed in November 2017 during the phase II trial, which included a total of 61 randomized patients (21 on Arm A, 19 on Arm B, and 21 on Arm C), to determine whether the trial should be stopped or whether one of or both Arm B and Arm C would be continued if the trial is not stopped. It was decided to discontinue Arm C based on the recommendation of CCTG Data and Safety Monitoring Committee after their review of interim analyses results. The trial was continued as a two-arm trial comparing Arm A to Arm B. The primary endpoint PFS for the original phase II trial became the secondary endpoint of the phase III trial and will be analyzed in the end of phase III trial together with other endpoints.

12.2 Study Endpoints and Analysis

The primary endpoint of the phase III component of this trial is overall survival (OS), defined as time from randomization to the date of death from any cause. If a patient has not died, OS will be censored on the date the patient last known as alive. All patients from Arms A and B, except those included in the phase II interim DCR analysis, will be included in the analysis based on the arm they were randomized. A stratified log-rank test adjusting for stratification factor at randomization will be the primary method to compare OS between Arms A and B.

Progression free survival (PFS), a primary endpoint for phase II component and secondary endpoint for phase III component, is defined as time from randomization to the date when relapse/progression or death is first observed. If a patient has not relapsed/progressed or died, PFS will be censored on the date of last disease assessment.

Objective response rate (ORR), a secondary endpoint for both phase II and III components of the study, is defined as the proportion of observed CR/PR among all randomized patients.

Response assessments:

- mRECIST will be used for ORR and PFS while iRECIST will be used for exploratory analyses of ORR and PFS.
- ORR and PFS as assessed by blinded independent central review (BICR) will be used; ORR and PFS based on investigator assessment will be used as sensitivity analyses and will also be published by CCTG.

ORR and PFS will be secondary endpoints to undergo formal statistical hypothesis testing, with details provided in Section 12.3 and 12.6. For PFS by BICR, the analysis method will be same as the primary endpoint of OS. For ORR by BICR, the stratified Miettinen and Nurminen's method (stratified based on the stratification factor) will be used for the comparison between the two treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported.

All patients who have received at least one dose of study treatment will be included in the safety analysis. The incidence of toxicities will be summarized by type of adverse event and severity. A Fisher's exact test will be used as needed to compare toxicities between the two arms.

12.3 Sample Size and Duration of Study

Phase II (original sample size calculation)

The median PFS for Arm A was estimated as 7.5 months. To detect an increase of median PFS to 11.5 months (HR=0.65) by one of the experimental treatment arms with 80% power at a 1-sided 0.2 level, a minimum of 63 events would be required to observe from the three treatment arms. The required number of events would be observed by accruing up to 126 patients (42 per arm) during 24 months of accrual with 8 months follow-up.

Phase III

The median OS for Arm A is estimated as 16 months. To detect an increase of median OS to 22.9 months (HR=0.70) by Arm B with 90% power at a 2-sided 0.05 level, a minimum of 334 events would be required to observe from two treatment arms. The required number of events would be observed by accruing a total of up to 430 patients during 34 months of accrual with 31 months follow-up. If the median OS for Arm A is 13.5 months as originally estimated, the total duration of the trial may be shortened from 65 months to 59 months. Assuming 10 patients would drop out earlier, the final sample size of randomized patients would be 440 (220 per arm).

If the success criterion for OS is met, 70% of its alpha (two-sided 0.035) will be passed to PFS by BICR and 30% of its alpha (two-sided 0.015) will be passed to ORR by BICR. The median PFS for Arm A is estimated as 7 months. To detect an increase of median PFS to 10 months (HR=0.70) by Arm B with 90.6% power at a 2-sided 0.035 level, a minimum of 376 events would be required to observe from two treatment arms with a total of 440 patients randomized, assuming an annual dropout rate of 13%. With 440 patients randomized, the power for ORR testing at a 2-sided 0.015 level is approximately 87.5% to detect a 17% difference between an underlying ORR of 43% in arm A and 60% in arm B.

Note: A total of 520 patients will be enrolled: 440 to phase III, 40 were enrolled to Arm A and B and included in the interim DCR analysis of the phase II component and 40 patients were enrolled to Arm C before that arm was closed to accrual. The primary analysis population for the phase III analysis will exclude the 40 participants from the phase II Arms A and B that were included as part of the phase II interim analysis. Arm C patients are also excluded.

12.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported bi-annually at investigators' meetings.

The CCTG DSMC will review progress, safety (including SAEs and fatal SAEs) and planned interim analyses bi-annually.

12.5 Interim Analysis

Phase II

An interim analysis was performed when 22 patients on each treatment arm had been evaluated for 16 weeks disease control (DC) status (percentage of patient's with CR, PR and SD at 16 weeks). If the DC rate in Arm B or C was no worse than the control arm (Arm A), we would continue to full accrual. Otherwise, the accrual to the arm with DC rate worse than Arm A will be stopped. If the DC rates in both Arms B and C were worse than the control arm, the trial would be stopped. Assuming a 70% DC rate on control arm (Arm A) at 16 weeks, if the DC rate in one of the experimental arms is 16 % or better we would have an 80% chance of proceeding to trial with at least one experimental arm.

Phase III

The interim efficacy analysis will be conducted on OS, PFS and ORR 11 months after last patient is randomized.

Early termination will be considered when the two-sided p-value of the stratified log-rank test for the comparison of OS between two treatment arms is significant as indicated by the methodology of Lan-DeMets with O'Brien-Fleming type boundaries. The nominal significant value for the final analysis of OS will be adjusted based on actual number of events observed to ensure the overall type I error of OS hypothesis testing is controlled at a two-sided 0.05 level.

12.6 Multiplicity

The trial uses the graphical method of Maurer and Bretz *[Mauer 2013]* to control multiplicity for multiple hypotheses as well as interim analyses. Figure 1 shows the initial two-sided α allocation for each hypothesis in the ellipse representing the hypothesis.

PFS by BICR will be tested only when the hypothesis test for OS is significant, either at time of the OS interim analysis or the final analysis. The stratified log-rank test for the comparison of PFS between the two treatment arms will be used to indicate the statistical significance using the methodology of Lan-Demets with O'Brien-Fleming type boundaries. In the scenario that PFS events accrue slower than expected, and the observed number of events is less than the expected number of events, the final analysis for PFS will use the remaining Type I error that has not been spent at the interim analysis. The nominal significance value for the interim and final analyses of PFS will be adjusted based on the actual number of events observed to ensure that the type I error of testing PFS upon success of the OS hypothesis testing is controlled at a two-sided 0.035 level.

ORR by BICR will be tested at the interim analysis at 0.015 alpha level (2-sided) if OS hypothesis is rejected at the interim analysis. Note that if the OS hypothesis is not rejected at the interim analysis but at the final analysis, then the 0.015 alpha (2-sided) will be rolled over to ORR at the final analysis, but the test statistics previously computed at time of the interim analysis for the ORR hypothesis will be used for inferential testing to ensure that the type I error of testing ORR upon success of the OS hypothesis testing is controlled at a two-sided 0.015 level.

When the PFS hypothesis is rejected, its alpha can be further passed to ORR to be tested at the full two-sided 5% level; conversely, when the ORR hypothesis is rejected, its alpha can be further passed to PFS to be tested at the full two-sided 5% level.

The overall type I error of the trial is strictly controlled at a two-sided 0.05 level.

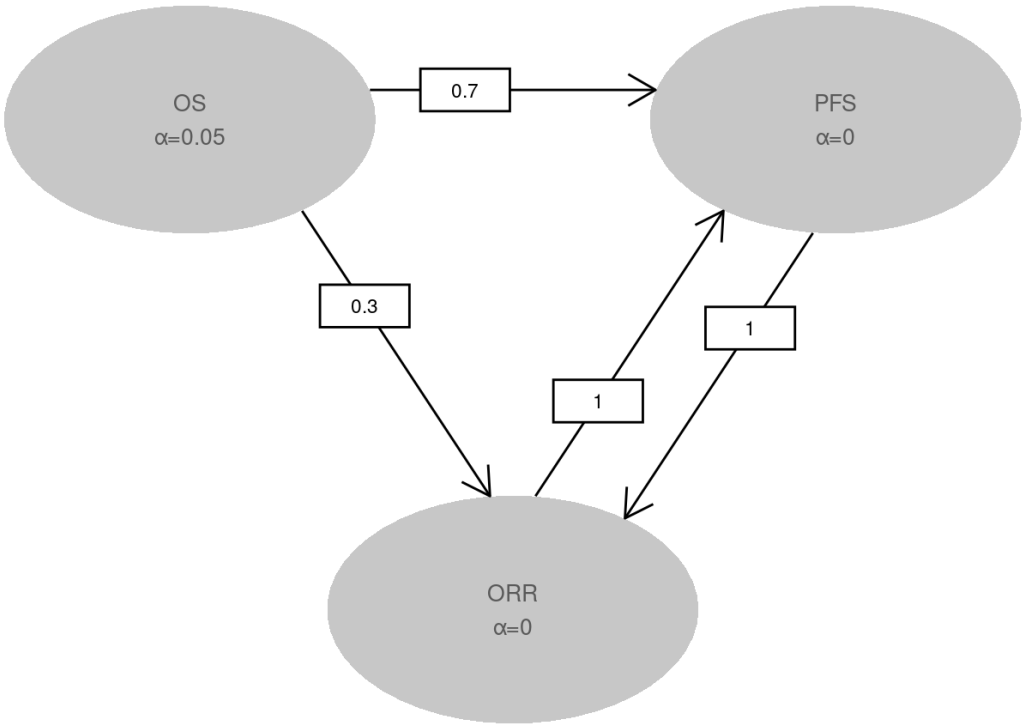


Figure 1 Multiplicity Graph for Type I Error Control

12.7 Quality of Life Analysis

The quality of life (QoL) of patients will be assessed using the EORTC QLQ-C30 core questionnaire *[Aaronson 1993]* and the lung cancer module (QLQ-LC13) *[Bergman 1994]*. Both instruments have been used extensively in studies involving patients with MPM, and in clinical trials assessing immune checkpoint inhibitors in the setting of non-small cell lung cancer.

The EORTC QLQ-C30 *[Aaronson 1993]* is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100. The QLQ-LC13 lung cancer module *[Bergman 1994]* includes questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The validity and reliability have been studied by the EORTC Study Group on Quality of Life. The EORTC QLQ-C30 and module will be scored according to the EORTC QLQ-C30 Scoring Manual, and analyzed accordingly.

Both the EORTC QLQ-C30 and QLQ-LC13 have demonstrated validity in patients with MPM *[Nowak 2004]*. In patients treated with platinum-based combination chemotherapy, there are no issues with floor or ceiling effects for symptoms typically associated with pleural-based disease. Fatigue is a common complaint but may not change much on treatment. Also common, and more obviously directly related to tumour location, are cough, dyspnea, and pain.

The primary endpoint of the QoL analysis is defined as the time from baseline to first deterioration in the following three common MPM symptoms: cough (Question 1 in QLQ-LC13), dyspnea (Question 8 in QLQ-C30), and chest pain (QLQ-LC-13, item 10). Patients will be considered as deteriorated for a given symptom if their change score from baseline was 10 points or worse at any time-point after baseline with a confirmation by a subsequent visit of a 10 point or worse deterioration. For each symptom, all patients who have a baseline and at least one follow-up QOL assessment for this symptom will be included in the time-to deterioration analysis. Patients will be censored at the time of the last QOL questionnaire completion if they had not deteriorated before that. The log-rank test will be the primary method to compare the time to deterioration in MPM symptoms between the two treatment arms. Time to deterioration in each of MPM symptoms will also be compared similarly and the Hochberg procedure *[Hochberg 1988]* will be used to adjust the *P* values of the log-rank tests for these three comparisons.

Changes in the quality of life scores while on treatment versus baseline will be examined using descriptive statistics and the standard CCTG QoL response analysis. Specific time points will be checked to explore treatment side effect on patients QoL, and the benefit of the study treatment. In addition, baseline scores will be compared using a Wilcoxon rank sum test, and a pattern mixture model *[Little 1995]* identifying drop-out patients as a special category, will be performed to evaluate the effect of missing data. PRO compliance summary, including completion and compliance rates of QLQ-C30 and LC13 will be described for patients with at least one dose of study treatment and at least one QOL assessment. Additional analyses will be conducted using CCTG standard analysis method *[Osoba 2011]*.

12.8 Economic Analysis

The purpose of the economic evaluation is to determine the incremental cost-effectiveness and cost-utility of pembrolizumab added to standard chemotherapy from a government payer perspective, over a lifetime time horizon by prospectively collecting economic and resource utilization information during the clinical trial. Medical costs will be censored using methods previously described *[Bang 2002]*.

The objectives are:

a) determine an incremental cost effectiveness ratio reported as a cost per life-year (LY) gained of pembrolizumab plus standard chemotherapy versus chemotherapy alone. The mean incremental survival using the restricted Kaplan Meier method and overall cost per patient for each of the two study treatment arms will be calculated to determine the addition cost per life-year gained.

b) determine an incremental cost utility ratio as a cost per quality-adjusted life-year (QALY) gained of pembrolizumab plus standard chemotherapy versus chemotherapy alone. Preference weights for comparator arms will be determined through the Canadian and European Valuation of the EQ-5D-5L Health States *[Xie 2016; Devlin 2017],* with EQ-5D scores taken directly from the study database. Quality-adjusted survival in the two treatment arms will be generated by multiplying the utility value by the amount of time spent in that utility state. The mean incremental cost per QALY between treatment arms will be calculated.

The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Major drivers of medical care costs, namely hospitalization, immunotherapy drug acquisition cost and survival, will be varied ± 20%, to examine the impact on the base-case incremental cost effectiveness ratios (ICERs). Patient preferences will also be varied across an acceptable range. A cost-effectiveness acceptability curve will be generated through bootstrapping samples. The economic data analysis will only include data from groups/regions that participate in the economic study. The CCTG and ISPOR recommendations for Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials will be followed *[Mittmann 2014; Ramsey 2015]*. Relevant subgroup analyses will be performed for clinical or biomarker-defined populations that benefit most from the novel therapy in the clinical trial. The net monetary benefit approach may be used as an alternative in the case of very small gains in QALY or OS.

13.0 PUBLICATION POLICY

13.1 Authorship of Papers, Meeting Abstracts, Etc.

13.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author(s) will generally be the chair(s) of the study.
- A limited number of the members of the Canadian Cancer Trials Group and National Cancer Institute Naples (NCI Naples) and IFCT may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

13.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

13.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results
CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

13.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by National Cancer Institute, Naples (NCI Naples), other participating Groups, the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

14.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

14.1 Regulatory Considerations

All institutions must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

In Canada this trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

Outside of Canada this trial is being conducted by academic groups who will act as sponsors and obtain all necessary approvals (regulatory, REB) for the conduct of an academic clinical trial in their countries.

14.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

14.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of certified translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

14.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CCTG.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/exposure. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an "Exposure Follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

14.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

14.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified/Principal Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

In Canada essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

In other countries the local sponsor Group will advise participating sites of the required period that essential documents must be retained according to national regulations.

14.6 Centre Performance Monitoring (All Sites)

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

14.7 On-Site Monitoring/Auditing Monitoring (All Sites)

Monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

Your site may be subject to an inspection by the Health Canada Inspectorate or other regulatory agencies.

The above mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

14.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates are to be found in Appendix III.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the IND.227 area of the CCTG web-site (www.ctg.queensu.ca).

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For more information on the EQ-5D questionnaire, please go to website www.euroqol.org.

APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Distribution
Pembrolizumab will be supplied by Merck & Co., Inc. to the distributor, and sent from the distributor to participating centres for non-Canadian sites. For Canadian sites, drug will be distributed by BARL

Drug Labelling
Pembrolizumab supplies for this study will be labelled in accordance with Health Canada Regulations and Italian regulations. The labels contain all information required under the drug labelling regulations.

Initial Drug Supply
Once a centre is locally activated (following receipt and review of all required documentation), CCTG will authorize a start-up supply of Pembrolizumab to be shipped directly to the centre. The drug will be shipped to the centre within 7 working days of local activation. Drug accountability and drug re-order forms will be included with the drug shipment and are also available on the trial website for IND.227.

Only pembrolizumab is supplied. Pemetrexed and cisplatin for this protocol are commercially available and sourced from the Canadian market and from the markets of other participating countries.

Drug Ordering (Re-supply)
Fax a copy of the pembrolizumab drug re-order form (available on the IND.227 website) to the distributer.

Please allow sufficient time for shipment of drug.

Drug Accountability
The investigational products are to be prescribed only by the investigator and co-investigators on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained accounting for the receipt of the investigational product and for the disposition of the product (Drug Accountability Log).

Drug Destruction or Return:
The CCTG Study Coordinator must be contacted prior to destruction of expired medication to ensure an extension of expiry date is not expected. Expired trial medication may be destroyed per local policy, AFTER accountability and reconciliation has been completed and documented by the site and confirmed with CCTG. Documentation of destruction must be kept on file in the site pharmacy and is subject to on site monitoring/audit.

**PLEASE NOTE **

DRUG FROM THIS SUPPLY IS TO BE USED ONLY

FOR PATIENTS REGISTERED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating centre.

APPENDIX III - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see Section 9 for details regarding SAE reporting). For details about accessing the EDC system and completing the on-line Case Report Forms, please refer to the Data Management Guidebook posted on the IND.227 area of the CCTG website (www.ctg.queensu.ca).

Electronic Folder	Required at	To be completed/submitted electronically	Supporting Documentation Required[1]	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Eligibility Checklist		Within 2 weeks of randomization	Signed consent form and tissue banking consent[2], surgical reports, diagnostic pathology reports, protocol-mandated baseline radiology reports, tumour measurement sheet (TMS), PD-L1 or genomic testing results (if done)	ECG, LVEF, QOL, additional clinical, laboratory or imaging reports that may impact on decision regarding eligibility
Baseline Report		Within 2 weeks of randomization		
Correlative Studies Report (Tumour and Blood)		Within 2 weeks of randomization, updated within 4 weeks of collection of correlative bloods		
Concomitant Medications Report	Continuous running-log folder			
Treatment Report	Every 21 days	Within 2 weeks of end of cycle	Radiology reports for protocol-mandated imaging and non-protocol mandated imaging if relevant to disease assessment, TMS	Radiology reports for other non-protocol mandated imaging, ECG, LVEF, QOL, additional clinical laboratory or imaging reports that may inform evaluation of safety
End of Treatment Report	End of treatment	Within 2 weeks of end of treatment		
4 Week Follow Up Report	4 weeks from end of last cycle	Within 2 weeks of 4 weeks visit	Radiology reports for protocol-mandated imaging, TMS	Radiology reports for other non-protocol mandated imaging . additional clinical laboratory or imaging reports that may inform evaluation of safety
Follow Up Report	Every 3 or 6 months (see Sections 5.0 and 10.4)	Within 4 weeks of visit	Radiology reports for protocol-mandated imaging, TMS	Radiology reports for other non-protocol mandated imaging copies of additional clinical, laboratory or imaging reports that may inform evaluation of safety
Relapse/Progression Report	Upon disease progression	Within 4 weeks of progression	Radiology reports for protocol-mandated imaging and pathology reports	Radiology reports for other non-protocol mandated imaging

table continues on next page ...

Electronic Folder	Required at	To be completed/submitted electronically	Supporting Documentation Required[1]	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Death Report	When patient dies	Within 4 weeks of patient's death	Autopsy report if performed	Additional clinical, laboratory or imaging reports that may inform evaluation of cause of death
SAE Report[3]	At the time of event and reported to CCTG	Within 1 working day		Additional clinical, laboratory or imaging reports that may inform evaluation of safety including, admission and discharge summaries/notes

1 Scan and upload into the EDC Supporting Document Upload Tool - please refer to the slide set on the IND.227 website for guidance. Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) as not submitted. All ~~relevant~~ patient identifiers, other than the CCTG patient ID assigned at enrolment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements. Acceptable methods include:

- **fully opaque** sticker/tab placed over the identifiers prior to scanning
- **fully opaque** black marker; prior to upload please ensure that the information is no longer visible on the scanned document
- electronic black box placed over identifiers in PDF document that is subsequently **printed and then** scanned. (*NOTE:* do not send the unprotected PDF file with black boxes included as those can be moved / removed easily after opening)
- electronic stripping of identifiers prior to upload (typically only possible for DICOM images)

Note that supporting documents must include the participant's trial code, CCTG patient serial number, and participant initials (or a two/three masking letter code assigned by your centre)

2 For Canadian centres: it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated. Centres are expected to redact the participant's name and signature on the submitted copy, leaving only a portion visible (e.g. initials or loops) to confirm that a person has signed but that cannot identify that individual. For all other centres: submission of consent forms is not required but they will be reviewed on site.

3 See Section 9.0 Serious Adverse Event Reporting for details.

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX V - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

Electronic copies of the Quality of Life Questionnaires are available on the IND.227 website in English, French (for Canada), and other required languages (for other participating countries).

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

1. additional and useful information may be obtained from quality of life measurements
2. a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

1. to try to achieve the best possible outcome for patients
2. to evaluate the extent of change in the quality of life of an individual or group across time
3. to evaluate new treatments and technologies
4. to support approval of new drug applications
5. to try to provide the best value for health care dollars
6. to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   1. pre-randomization or pre-registration (baseline)
   2. during treatment
   3. during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (up to 3 days prior to treatment is acceptable). If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French or relevant language)

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

   If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **IND.227**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

During Treatment:

☐ Day 1 cycle _____

Off Treatment:

☐ 4 weeks post end of protocol therapy

☐ Follow-up visit # _____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (IND.227)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body? If yes, where_____	1	2	3	4
43. Did you take any medicine for pain? 1 No 2 Yes If yes, how much did it help?	1	2	3	4

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VII - HEALTH UTILITIES ASSESSMENT

Introduction

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival and disease free survival into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" – including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations;
- to evaluate the extent of change in health benefits of an individual, group, or population across time;
- to evaluate new treatments, technologies, and patient management strategies;
- to support approval of new drug applications or patient management strategies;
- to try to provide the best value for health care dollars within and across diseases and health;
- to compare costs and benefits of various financial and organization aspects of health care services.

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

(see IND.227 webpage for questionnaire)

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

   Health utilities data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - Pre-registration (for this study, within 7 days prior to registration)
   - During treatment (day 1 each cycle)
   - During Follow up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g. psychological distress, social disruption, symptoms, side effects, etc.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

4. What If…

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. A couple of situations are described below.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. As the patient is s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic for completion.

5. Inability to Complete Health Utilities Questionnaire *(for reason other than illiteracy in English or French or relevant language)*

An eligible patient may be willing but physically unable to complete the questionnaire, because of blindness, paralysis, etc. If the patient is completing the EQ-5D assessment in the clinic, the questionnaire should be read to them and the answers recorded by the health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Health Utilities Index – ENGLISH

CCTG Trial: **IND.227**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

During Treatment:

☐ Day 1 cycle _____

Off Treatment:

☐ 4 weeks post end of protocol therapy

☐ Follow-up visit # _____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ___ ___ ___

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

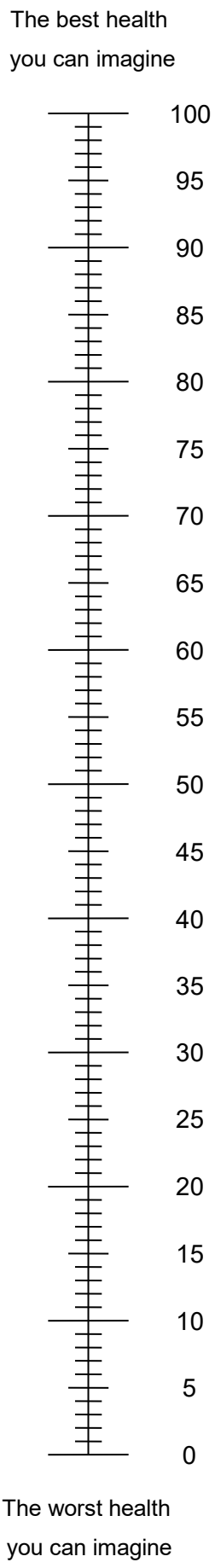
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX VIII - EMERGENCY SITUATIONS AND COMPLIANCE

1.0 Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

In these rare circumstances, minor deviations that do not impact patient safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB, and review the trial website for additional guidance specific to the trial. .

Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. *Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.*
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Patient care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*.

  **Must be approved by CCTG or acceptable per further instruction from CCTG.*
- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

LIST OF CONTACTS

PATIENT REGISTRATION
All patients must be registered with CCTG before any treatment is given.

	Contact	Tel. #	Fax #
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Joana Sederias or Kelsey Curran Study Coordinators, CCTG Emails: jsederias@ctg.queensu.ca kcurran@ctg.queensu.ca or Lesley Seymour Senior Investigator, CCTG Email: lseymour@ctg.queensu.ca	613-533-6430	613-533-2411
STUDY CHAIRS	Canada: Dr. Quincy Chu Study Chair Email: Quincy.Chu@albertahealthservices.ca		
	Italy: Dr. Francesco Perrone Email: f.perrone@istitutotumori.na.it		
	France: Dr. Laurent Greillier Email: laurent.greillier@ap-hm.fr		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Lesley Seymour Senior Investigator, CCTG or Joana Sederias or Kelsey Curran Study Coordinators, CCTG	613-533-6430	613-533-2411
DRUG ORDERING See Appendix II for full details.	See Appendix II and IND.227 website for details and contact information		
ELECTRONIC DATA CAPTURE (EDC) AND RIPPLE (technical support)	CCTG Home Page (Toolbox): https://scooby.ctg.queensu.ca Email Support Staff at: support@ctg.queensu.ca		