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CCTG TRIAL: IND.225

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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II STUDY OF THE ASSESSMENT OF RESPONSE TO PEMBROLIZUMAB IN METASTATIC MELANOMA: CT TEXTURE ANALYSIS AS A PREDICTIVE BIOMARKER

CCTG Protocol Number: **IND.225**

STUDY CHAIR: Teresa Petrella

SENIOR INVESTIGATOR: Janet Dancey

SENIOR BIOSTATISTICIAN: Bingshu Chen

STUDY COORDINATOR: Linda Hagerman

REGULATORY SPONSOR: CCTG

SUPPORTED BY: Merck

(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 Merck.

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 and that 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 and Merck 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 Merck and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Merck and 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 or Merck with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Merck and 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.225

CENTRE: _____

TREATMENT SCHEMA

Eligibility Criteria

- Histologically confirmed melanoma that is recurrent/metastatic and not amenable to potentially curative surgery;
- Clinically and/or radiologically documented disease with at least one site of disease unidimensionally measurable by contrast-enhanced CT scan;
- Radiology must be performed within 28 days prior to registration (35 days if negative);
- Age ≥ 18 years;
- ECOG 0 to 1;
- Previous surgery permitted as long as 21 days prior to patient registration and wound healing has occurred;
- Palliative radiation permitted as long as >7 days between last dose and enrolment on trial;
- Neutrophils ≥ 1.5 x 10^9/L;
- Platelets ≥ 100 x 10^9/L;
- Hemoglobin ≥ 90 g/L or ≥ 5.6 mmol/L (without transfusion or EPO dependency);
- Serum creatinine ≤ 1.5 x ULN **OR** measured or calculated creatinine clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 x ULN;
- Serum total bilirubin ≤ 1.5 x ULN **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN;
- AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver mets);
- Albumin ≥ 25 g/L;
- Negative serum or urine pregnancy test within 7 days prior to registration (if applicable);
- Men and women of child-bearing potential must use adequate contraception as described in Section 5.1.7.

Ineligibility Criteria

- Prior systemic therapy for metastatic melanoma;
- Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies);
- Known history of or known positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected). Patients with unknown history of HBV or HCV will require screening;
- Patients with previously treated brain metastases may participate provided they are stable with no evidence of enlargement following radiation treatment and no acute radiation toxicity **OR** no evidence of enlargement at least 4 weeks prior to the first dose of study drug if untreated and are off systemic steroids for at least two weeks;
- Patients who are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study;

- Patients who previously had a severe hypersensitivity reaction to treatment with another mAb;
- Patients with an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents;
- Patients with a history of a malignancy (other than the disease under treatment in the study) within 5 years prior to first study drug administration;
- Patients on any systemic corticosteroid therapy within one week before the planned date for first dose of treatment or on any other form of immunosuppressive medication;
- Patients with an allergy to iodinated contrast media used for CT;
- Patients with a known history of active TB (Bacillus Tuberculosis);
- Patients with evidence of interstitial lung disease;
- Patients with known history of, or any evidence of active, non-infectious pneumonitis.

Pre-Treatment Evaluations

- History, physical exam, ECOG performance status, vital signs, toxicity/baseline symptoms (within 14 days prior to registration);
- Hematology and biochemistry (within 7 days prior to registration);
- Pregnancy test (within 7 days prior to registration, if applicable);
- ECG (within 7 days prior to registration if not done within 6 months);
- Health Utilities Index (EQ-5D) (within 7 days prior to registration);
- CT scan with contrast of chest, abdomen/pelvis (within 28 days prior to registration; 35 days if negative).

Treatment

- Pembrolizumab will be given intravenously day 1 every 3 weeks

On-Treatment Evaluations

- History and physical exam, ECOG (Day 1 each cycle)
- Vital signs (blood pressure and pulse) (Day 1 each cycle)
- Hematology and Biochemistry (Day 1 each cycle)
- TSH, FT3, FT4 (every other cycle)
- CT scan with contrast of chest, abdomen/pelvis (4 weeks, 12 weeks, then every 12 weeks)
- ECG (as clinically indicated)
- Health Utilities Index (EQ-5D) and Resource Utilization Assessment (each 12 weekly visit until progression OR maximum 1 year from registration)
- Adverse events – patients to be evaluated continuously for adverse events.

Duration of Treatment

See Section 12.

1.0 OBJECTIVES

1.1 Primary Objective

To assess whether tumour texture parameters from a CT scan can differentiate patients who do and who do not respond to treatment with pembrolizumab.

1.2 Secondary Objectives

- To assess whether tumour texture parameters from a CT scan can correlate with time to disease progression in patients with metastatic melanoma being treated with pembrolizumab.
- To assess duration of response (DoR).
- To assess overall response rate (ORR, PR, CR).
- To assess overall survival (OS).
- To compare cost per quality adjusted life years (QALY) between pembrolizumab and dacarbazine.
- To compare cost per quality adjusted life years (QALY) between pembrolizumab and ipilimumab.
- Toxicity using the CTCAE v.4.

2.0 BACKGROUND INFORMATION AND RATIONALE

Metastatic melanoma historically has had a very poor survival. Thankfully this is now changing due to advent of new targeted drugs and breakthroughs in immunotherapy. Programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. Its ligand, PD-L1 is frequently expressed within the tumour microenvironment including tumour cells. Tumour models have shown that PD-1 negatively regulates the effector phase of T-cell responses after ligation of PD-L1 expressed within the tumour *[Blank 2004]*. Several drugs have been developed that block PD-1 and hence augment the T cell response. The most mature results have been obtained in advanced melanoma patients and indicate high response rates, high quality responses and prolonged duration of response and prolonged survival.

Pembrolizumab is a highly selective, humanized monoclonal IgG4-kappa isotype antibody against PD-1 that is designed to block the negative immune regulatory signalling of the PD-1 receptor expressed by T cells *[Hamid 2013]*. Pembrolizumab has shown improved response rates, response duration and survival compared to standard treatments for melanoma *[Ribas 2015; Patnaik 2014]*. Patients receiving pembrolizumab had an overall RR of 38% with durable responses and approximately a further 30% of patients with disease control. The 1 year survival in this trial was 67% and 50% at 2 years in patients with metastatic melanoma *[Daud 2015]*. Pembrolizumab was also compared to ipilimumab in first line therapy for metastatic melanoma and showed a better RR and OS rate compared to ipilimumab with a RR of 34% compared to 12% and OS at 12 months of 74% compared to 58% for ipilimumab *[Robert 2015]*. In this study and subsequent phase III studies, pembrolizumab is administered intravenously at 2 mg/kg every 2 weeks for a total of 2 years. Recent results from pharmacokinetic studies indicate that a flat dose of 200 mg IV is sufficient for exposure and that there is no additional advantage to weight-based dosing. In addition, responses occur early within the first 8 weeks and it is possible that 2 years of consecutive therapy may not be needed given the durable responses seen with ipilimumab short courses.

Imaging is widely used in oncology for confirmation of diagnosis, staging and assessing treatment response. Tumour heterogeneity, such as heterogeneity of the tumour blood supply is a well-recognized feature of malignancy. Computed tomographic (CT) texture analysis is a form of quantitative feature analysis that focuses on the heterogeneity of attenuation within tumours *[Goh 2011]*. Evidence suggests that texture analysis has the potential to augment diagnosis by differentiating between benign and malignant neoplasms, tumour staging by differentiating between invasive and non-invasive disease and malignant/non-malignant lymph nodes, and therapy response assessment in oncological practice *[De Ruysscher 2013; Bayanati 2014]*. Characteristics such as textural heterogeneity on a CT scan have been used to predict response and time to progression in renal cell carcinoma (RCC) and non-small cell lung carcinoma (NSCLC) patients *[Goh 2011; Win 2013]*. In metastatic renal cell cancer patients on TKIs, texture analysis was shown to be an independent factor associated with time to progression *[Goh 2011]*.

Our investigators have previously evaluated and confirmed the prognostic value of texture analysis in RCC. To our knowledge the potential of texture analysis has not been explored in patients with metastatic melanoma. However, its application in patients with advanced melanoma who are candidates for immunotherapy is reasonable and may be quite valuable. We hypothesize that texture analysis will differentiate responders/non-responders to pembrolizumab and differentiate between pseudoprogression from true disease progression. The benefits of imaging biomarker would be several: identification of patients for treatment, early discontinuation for failure of response, and appropriate continuation of treatment in patients with pseudoprogression. By limiting the numbers of patients receiving treatment that are not benefiting, the overall cost effectiveness of treatment and overall benefit to Canadian patients and the Canadian health care system is increased.

We are proposing a phase II study in metastatic melanoma patients treated with pembrolizumab 200 mg IV q 3 weeks to assess whether tumour texture parameters from a CT scan can differentiate time to progression and response. Patients will be followed on study for a maximum of 12 months. The trial will be sponsored and conducted by the Canadian Cancer Trials Group, Canada's largest adult cooperative cancer clinical trials group. The group has conducted more than 400 phase I-III trials in all cancer settings and all modalities of treatment. The Melanoma Disease Site Committee of the CCTG has successfully conducted several early phase clinical trials testing novel treatments in melanoma at cancer centres across the country. The group will collaborate with experienced imaging researchers at Sunnybrook and OICR to ensure quality of acquisition and interpretation of CT images.

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

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

3.0 BACKGROUND THERAPEUTIC INFORMATION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.0 TRIAL DESIGN

This is an open-label, multicentre, phase II trial of pembrolizumab in first line therapy of metastatic melanoma. This trial is being conducted by the Canadian Cancer Trials Group with the support of Merck.

5.0 STUDY POPULATION

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

5.1 Eligibility Criteria

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

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:

5.1.1 Histologically confirmed melanoma that is recurrent/metastatic and not amenable to potentially curative surgery.

5.1.2 Presence of clinically and/or radiologically documented disease based on RECIST 1.1. At least one site of disease must be unidimensionally measurable by contrast-enhanced CT scan as follows:

CT scan (with slice thickness of $\leq$ 5 mm)	$\geq$ 10 mm	→ longest diameter
Lymph nodes by CT scan	$\geq$ 15 mm	→ measured in short axis

All radiology studies must be performed within 28 days prior to registration and meet the criteria outlined in Appendix VI (exception: within 35 days if negative).

5.1.3 Age $\geq$ 18 years.

5.1.4 ECOG Performance Status of 0 to 1.

5.1.5 *Previous Therapy*

Surgery:
Previous surgery is permitted provided that it has been at least 21 days prior to patient registration and that wound healing has occurred.

Systemic Therapy:
Patients may not have received any prior systemic therapy for metastatic melanoma.

Radiation:
Palliative radiation is permitted provided > 7 days has elapsed between last dose and enrollment on the trial.

5.1.6 *Laboratory Requirements* (must be done within 7 days prior to registration)

Hematology:	Absolute neutrophils (ANC)	$\geq 1.5 \times 10^9$/L
	Platelets	$\geq 100 \times 10^9$/L
	Hemoglobin	$\geq$ 90 g/L or $\geq$ 5.6 mmol/L (without transfusion or EPO dependency)
Chemistry:	Serum creatinine	$\leq$ 1.5 x ULN
	OR	**OR**
	Measured or calculated creatinine clearance	$\geq$ 60 mL/min for subject with creatinine levels > 1.5 x ULN
	Serum Total Bilirubin	$\leq$ 1.5 x ULN
	OR	
	Direct bilirubin	$\leq$ ULN for subjects with total bilirubin levels > 1.5 x ULN
	AST and ALT	$\leq$ 2.5 x ULN ($\leq$ 5 x ULN for subjects with liver mets)
	Albumin	$\geq$ 25 g/L

5.1.7 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method. 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.

5.1.8 Women of childbearing potential will have a serum or urine pregnancy test within 7 days prior to registration to determine eligibility. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. This may also include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin 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.

5.1.9 Patient consent must be obtained according to local Institutional and/or University Human Experimental Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the CCTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is provided on the IND.225 webpage. A copy of the initial REB approval and approved consent form must be sent to the central office. The patient must sign the consent form prior to registration and prior to tests which are considered to be study specific (see Section 6). Please note that the consent form for this study must contain a statement which gives permission for the CCTG and monitoring agencies to review patient records.

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.

5.1.10 Patients must be accessible for treatment 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.) Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

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

5.2 Ineligibility Criteria

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

5.2.1 Patients who have received prior systemic treatment for metastatic melanoma.

5.2.2 Patients with known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

5.2.3 Patients with a known history of or known positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected). Patients with unknown history of HBV or HCV will require screening.

5.2.4 Patients with previously treated brain metastases may participate provided they are stable with no evidence of enlargement following radiation treatment and no acute radiation toxicity OR no evidence of enlargement at least 4 weeks prior to the first dose of study drug if untreated and are off systemic steroids for at least two weeks.

5.2.5 Patients who are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the pre-screening or screening visit through 4 months after the last dose of trial treatment.

5.2.6 Patients who previously had a severe hypersensitivity reaction to treatment with another mAb.

5.2.7 Patients with an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. (Only patients on active treatment are ineligible).

5.2.8 Patients with a history of a malignancy (other than the disease under treatment in the study) within 5 years prior to first study drug administration.

5.2.9 Patients on any systemic corticosteroid therapy within one week before the planned date for first dose of treatment or on any other form of immunosuppressive medication.

5.2.10 Patients with an allergy to iodinated contrast media used for CT.

5.2.11 Patients with a known history of active TB (Bacillus Tuberculosis).

5.2.12 Patients with evidence of interstitial lung disease.

5.2.13 Patients with known history of, or any evidence of active, non-infectious pneumonitis.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	• history • height/weight • vital signs (blood pressure and pulse) • ECOG performance status • documentation of all measurable and non-measurable disease • clinical tumour measurements (if applicable)	Within 14 days prior to registration
Hematology	• CBC, differential, platelets	Within 7 days prior to registration
Biochemistry	• serum creatinine (or measured or calculated creatinine clearance) • electrolytes (sodium, potassium, chloride, bicarbonate) • bilirubin • alkaline phosphatase • AST, ALT • LDH • phosphorous • calcium • magnesium • albumin • TSH, FT3, FT4 • HCV, HBV screening serology (if unknown)	Within 7 days prior to registration
Radiology[1]	• CT scan with contrast of chest, abdomen/pelvis • other sites as clinically indicated	Within 28 days[2] prior to registration
Other Investigations	• pregnancy test* (if applicable)	Within 7 days prior to registration
	• ECG (if not done within 6 months)	
Economics	• Health Utilities Index (EQ-5D)	
Adverse Event[3]	• baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	

1 To ensure comparability, baseline and subsequent CT scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner – see Appendix VII).

2 Thirty-five days if negative

3 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

* These tests are considered study-specific and must be performed AFTER the informed consent form has been signed.

7.0 ENTRY/REGISTRATION PROCEDURES

7.1 Entry Procedures

All registrations 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 registering 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.225 trial specific web-site. If sites experience difficulties accessing the system and/or registering patients please contact the help desk (link in EDC) or the IND.225 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.225)
- 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 5.0, including dates of essential tests and actual laboratory values
- height and weight

7.2 Registration

Registrations 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 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 registration.

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

8.0 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.

8.1 Chemotherapy Treatment Plan

8.1.1 *Drug Administration*

Agent	Route	Starting Dose	Schedule
Pembrolizumab	IV	200 mg	Day 1 every 3 weeks

8.2 Dose Adjustments for Pembrolizumab

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life threatening AEs as per Table below.

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.

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.

8.3 Dose Modification Guidelines for Drug-related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. Insulin replacement therapy is recommended for Type I diabetes mellitus and for grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

table continued on next page …

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1. For grade 2 events treat with systemic corticosteroids. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Section 8.3.1, Infusion Related Reactions Table for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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.

8.3.1 *Infusion Related Reactions*

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

8.4 Duration of Protocol Treatment

Treatment will continue until the criteria for removal from protocol treatment have been met (see Section 12.0).

8.5 Concomitant Therapy

8.5.1 *Permitted*

Patients may receive ongoing supportive and palliative care (e.g. pain control) as clinically indicated throughout the study. Physiological doses of systemic corticosteroids are allowed, as well as inhaled, topical and prophylaxis use for allergic reactions, such as IV contrast dye. All supportive medications must be recorded on the electronic case report form as appropriate.

8.5.2 *Not Permitted*

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy including corticosteroids (see Section 8.5.1), except for treatment of potential immune-related AEs during the study.
- Investigational agents other than pembrolizumab.
- Radiation therapy (Note: radiation therapy to a symptomatic solitary lesion may be allowed after consultation with CCTG). Radiation to target lesions should be avoided and if required, patient would be considered to have progressive disease.
- Live vaccines within 30 days prior to the first dose of study therapy and while on study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

9.1 Evaluation During Protocol Treatment

Investigations		Timing
History and Physical Exam including:	• history • weight • ECOG Performance status • vital signs (blood pressure and pulse) • clinical tumour measurements (if applicable)	Day 1 each cycle
Hematology*	• CBC, differential, platelets	Day 1 each cycle
Biochemistry*	• electrolytes (sodium, potassium, chloride, bicarbonate) • alkaline phosphatase • AST, ALT • serum creatinine • bilirubin	Day 1 each cycle
	• phosphorous • calcium • magnesium • albumin	As clinically indicated
	• TSH, FT3, FT4	Every other cycle
Radiology**	• CT scan with contrast of chest, abdomen/pelvis • Other sites as clinically indicated	4 weeks, 12 weeks, then every 12 weeks
Other Investigations	• ECG	As clinically indicated
Economics	• Health Utilities Index (EQ-5D) • Resource Utilization Assessment	To be completed at each 12 weekly visit until progression OR maximum 1 year from registration
Adverse Events***	Patients must be evaluated after each cycle for adverse events	

* Bloodwork Timing: Pre-treatment blood draws should be done within 72 hours (maximum) prior to treatment.

** Patients with a CR or PR should have scans repeated after minimum 4 weeks to confirm response. See Appendix VII for CT requirements.

*** Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

9.2 Evaluation After Protocol Treatment

All patients will be seen at 4 weeks after the end of the last cycle date. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies). Patients who go off protocol therapy before progression is documented or have objective CR, PR or SD ongoing, follow-up and a Follow-up Report will be required at least every 3 months for a maximum of 1 year, (See Appendix I for investigations to be performed). Death Report will be required for all patients. Due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).

Investigations		Timing
History and Physical Exam including:	• history • weight • ECOG Performance status • vital signs (blood pressure and pulse) • clinical tumour measurements (if applicable)	4 weeks post end of last cycle
Hematology	• CBC, differential, platelets	4 weeks post end of last cycle
Biochemistry	• electrolytes (sodium, potassium, chloride, bicarbonate) • alkaline phosphatase • AST, ALT • serum creatinine • bilirubin	4 weeks post end of last cycle
	• phosphorous • calcium • magnesium • albumin	As clinically indicated
Radiology*	• CT with contrast of chest, abdomen and pelvis	As per standard of care (at least every 3 months) until progression or a maximum of 1 year
Other Investigations	• ECG	As clinically indicated
Adverse Events	Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).	4 weeks post end of last cycle
* Patients with a CR or PR should have scans repeated after minimum 4 weeks to confirm response.		

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

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

10.1.2 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 2016]*.

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as the modified iRECIST guidelines *[Seymour 2016]*. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

10.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee.

10.2.1 *Measurable Disease*. Measurable *tumour lesions* 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 ≥ 15mm 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.

10.2.2 *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.

10.2.3 *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 (see 10.2.4). 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. **Note: For this study, skin lesions will be considered as non-target lesions.**

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 can not 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.

10.2.4 *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.**

10.2.5 *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 < 10 mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10 mm) 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. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Patients that are clinically well may continue on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of PD by immune response criteria *[Seymour 2016]*. In this situation, patients do not have unequivocal progression until immune response criteria are met (see Table 2 below).

Table 1: 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.				

Immune-Related Response Assessment

Overall response will also be assessed using iRECIST *[Seymour 2016]*. 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 2: 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 3: 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.

10.3 Response Duration (RECIST 1.1 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).

10.4 Stable Disease Duration

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

10.5 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".

10.5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm 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.

10.5.2 *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.

10.5.3 *CT, MRI*. For this protocol the baseline CT scans within the first 12 weeks must conform to the requirements outlined in Appendix VII. For assessment of response using RECIST 1.1, 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. Other specialized imaging or other techniques may also be appropriate for individual case [ref RECIST 1.1]. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the CT conforms to Appendix VII.

10.5.4 *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.

10.5.5 *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.

10.5.6 *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.

10.5.7 *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.

10.6 Time to Tumour Progression

Time to tumour progression will be measured from date of registration until documented progression or death.

10.7 Overall Survival

Overall survival will be calculated from date of registration until death.

10.8 Censoring

Patients alive without progression at end of study will be censored at last visit/known to be alive and progression free.

11.0 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' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events, regardless of whether they are unexpected or related to protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported in an expedited manner. Any late deaths related to protocol treatment or other serious adverse event occurring after this 30-day period which is unexpected and related to protocol treatment must also be reported in an expedited manner (see Section 11.2 for reporting instructions).
- Known drug related events are excluded from expedited reporting unless they cause hospitalization, death or are life threatening
- SAE's that are considered definitely related to disease are excluded from expedited reporting but must be reported as adverse events
- 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

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.

11.2 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.225 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:

Linda Hagerman, 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. 225 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).

11.3 Other Protocol Reportable Events – Pregnancy Reporting

11.3.1 *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 Criterion 5.1.7. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

11.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 4 months after the completion of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy 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. 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.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The 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).

11.5 CCTG Reporting Responsibility to Merck

Merck will be notified of all protocol reportable serious adverse events (as defined in Section 11.1), via CIOMS report within 2 working days of receipt of report at CCTG. CCTG, as sponsor, will determine regulatory reportability in Canada.

11.6 Merck Reporting Responsibilities

Merck will report all regulatory reportable serious adverse events from non-CCTG trials (Safety Updates) with pembrolizumab to CCTG within the timelines outlined in the contract. CCTG will review these events to determine which meet the criteria (serious, unexpected, drug related) for reporting to IND.225 investigators. Merck will report these events to Health Canada.

11.7 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 in Canada 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.225 web-based safety monitoring utility.

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.225 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.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which 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 8.0.
- Tumour progression or disease recurrence as defined in Section 10.0.
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. 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.

12.2 Duration of Protocol Treatment

Maximum 1 year or until one or more criteria in Section 12.1 are met. After 1 year, patients may continue on pembrolizumab but will transition to standard of care management.

12.3 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment

See Section 9.2.

13.0 CENTRAL REVIEW PROCEDURES

13.1 Central Radiology Review

At the conclusion of the trial, a central review of x-rays and/or scans will be carried out for response. CT scans will be reviewed and analyzed for texture analysis. For purposes of reporting, the results of both local and central radiology reviews will be included.

13.2 Central Pathology Review

There will be no central pathology review for this study.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This is an open-label, multicentre, phase II trial of pembrolizumab in first line therapy of metastatic melanoma. The primary objective is to assess whether tumour texture parameters from a CT scan correlates with response in metastatic melanoma patients treated with pembrolizumab. Secondary end points include duration of response, overall response rate and survival.

14.2 Sample Size and Duration of Study

This is the first trial to evaluate tumour texture parameters to correlate them with tumour response to pembrolizumab.

Without knowing the true fraction of patients with CT features that are considered “positive” or “negative” it is not possible to do a true power calculation and the trial should be viewed as exploratory assessment of the potential of texture parameters to correlate with response. However, assuming the response rate to pembrolizumab is 35%, then a sample size of 80 patients will allow analysis of CT texture analysis parameters among 20-25 responding patients versus 55-60 non-responding patients. We propose to recruit 84 patients to identify 80 evaluable patients to assess for texture parameters in responders and non-responders which may support further evaluation in definitive trials. Sensitivity, specificity, positive and negative predictive values will be assessed.

Accrual rate is anticipated to be approximately 5-10 patients/month for total duration of accrual of 6-12 months.

Patients will be followed on study for the duration as indicated in Section 12.

14.3 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings. Adverse events will be categorized using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The worst event for each patient in each category or subcategory will be described. Both events related and unrelated to treatment will be captured.

Clinical and laboratory data will be tabulated and compared to normal ranges for the institution.

14.4 Economic Analysis

The purpose of the CCTG economic evaluation in this phase II study is to determine the incremental cost-effectiveness and cost-utility of pembrolizumab from a universal access government payer perspective, over a lifetime time horizon by prospectively collecting resource utilization information during this clinical trial and comparing to data collected from public databases.

In this study, a cost-utility analysis will be conducted to compare the overall cost per quality-adjusted-life-year (QALY) for pembrolizumab individually with dacarbazine and ipilimumab. Case report forms will be used in this study to document non-protocol based health care resource utilization over the course of treatment and follow-up, including outpatient consultations/visits/investigations, inpatient admissions, emergency room visits, supportive care medication for management of toxicity, and investigations/admissions/treatment of adverse events and disease progression. Forms will be ascertained at 12-week intervals while on treatment until disease progression or a maximum period of 12 months. Unit costs for drugs, hospitalizations, and treatments will be ascertained using publically available sources and reported in adjusted Canadian dollars.

Patient preferences while on pembrolizumab, or utilities, will be derived from the EQ-5D questionnaire *[Brooks 1996; Drummond 1997; www.euroqol.org]*. The EQ-5D self-administered questionnaire consists of two pages comprising the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and each dimension comprises three levels (no problems, some/moderate problems, extreme problems). The five level score may also be used. A unique EQ-5D health state is defined by combining one level from each of the five dimensions. The EQ 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. EQ-5D will be obtained at prescribed intervals. Utilities for patients on dacarbazine and ipilimumab will be obtained from published literature *[Tomme 2014]*.

A decision analytic Markov model will be used to extrapolate the costs and survival estimates from the current study (for pembrolizumab) and dacabazine/ipilimumab in order to generate cost/life-year estimates over clinically plausible scenarios. Survival estimates for dacarbazine and ipilimumab will be obtained from previously published randomized controlled trials *[Robert 2011]*. Life-year estimates will be multiplied by time-weighted utility values to generate QALYs. Use of pembrolizumab will be individually compared with dacarbazine and ipilimumab to generate incremental cost effectiveness ratios (ICERs) expressed as cost/QALY.

Deterministic and probabilistic sensitivity analyses using Monte Carlo simulations will be used to explore the robustness of the model to clinically plausible variations in key assumptions and variations in the analytical methods used. Major drivers of medical care costs, including hospitalizations, drug costs, and survival, will be varied +/- 20% and based on reported estimates provided in the literature. Cost effectiveness acceptability curves will be used to understand the impact of different thresholds of cost effectiveness and increase generalizability of results.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

15.1.1 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 will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and Merck, 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.

15.1.2 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)."

15.2 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).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by Merck, 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.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

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

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).

16.2 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.

16.3 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 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.

16.3.1 *Obtaining Consent for Pregnancy Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) 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" 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).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy. 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), consent must be obtained from the parent/guardian.

16.4 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.

16.5 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 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.

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.

16.6 Centre Performance Monitoring

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.

16.7 On-Site Monitoring/Auditing

CCTG site 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).

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

16.8 Case Report Forms

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

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. 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.225 area of the CCTG web-site: www.ctg.queensu.ca.

17.0 REFERENCES

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

APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study (within 7 days prior to registration, or as noted)	Day 1 each cycle	As clinically indicated	Every 12 weekly visit	4 wks, 12 wks then every 12 weeks	4 Weeks post treatment
History & Physical Exam						
Height and Weight	X[1]	X				X
ECOG Performance Status	X[1]	X				X
Vital signs (blood pressure and pulse)	X[1]	X				X
Documentation of all measurable and non-measurable disease	X[1]				X	X (if applicable)
Clinical tumour measurements (if applicable)	X[1]	X			X	X (if applicable)
Hematology & Biochemistry[2]						
CBC, differential, platelets	X	X				X
Serum creatinine, sodium, potassium, chloride, bicarbonate, bilirubin, ALP, AST, ALT, LDH[3],	X	X				X
Phosphorous, calcium, magnesium, albumin	X		X			
TSH, FT3, FT4	X	X[4]				
HCV, HBV screening serology (if unknown)	X					
Other Investigations						
Pregnancy test, *in women of childbearing potential only*	X					
ECG	X[5]		X			
Economics						
Health Utilities Index (EQ-5D)	X			X[6]		
Resource Utilization Assessment				X[6]		
Radiology						
CT scan with contrast of chest, abdomen/pelvis Other sites as clinically indicated	X (within 28 days prior to registration; 35 if negative)				X[7]	X[8]
Adverse Events						
Adverse Events/ Baseline Symptoms[9]	X	Continuously each visit				X

1 Within 14 days prior to registration.

2 Bloodwork Timing: Pre-treatment blood draws should be done within 72 hours (maximum) prior to treatment.

3 LDH is not required after baseline.

4 Every other cycle

5 Only required if not done within 6 months prior to registration

6 Each 12 weekly visit until progression OR maximum 1 year from registration

7 Patients with a CR or PR should have scans repeated after minimum 4 weeks to confirm response

8 All patients will be seen at 4 weeks after the end of last cycle date. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies). For patients who go off protocol therapy before progression is documented or have objective CR, PR or SD ongoing, follow-up and a Follow-up Report will be required at least every 3 months for a maximum of 1 year. A Death Report will be required for all patients.

9 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) *(Appendix V)*.

APPENDIX II - 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 III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution

Full details on Drug Distribution will be posted on the IND.225 webpage.

Pembrolizumab will be supplied by Merck to the distributor, and sent from the distributor to the participating centres.

Drug Labelling

Drug for this study has been labelled in accordance with Health Canada regulations.

Initial Drug Supply

Once a centre is locally activated (following receipt and review of all required documentation), the 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 5 working days of local activation. Note: Shipment will not be made on Fridays and weekends.

Drug accountability forms will be posted on the trial website.

Drug Ordering (Re-Supply)

Subsequent requests for more drug should be made by authorized personnel at each centre as directed on the supplied CCTG Request for Drug Shipment form. The drug re-order form can be found on the IND.225 website.

Please allow sufficient time for shipment of drug.

Note: Shipment will not be made on Fridays and weekends. Drug accountability and drug re-order forms will be posted on the trial website for pharmacists to download.

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

Expired/used study drug may be destroyed as per local standard operating procedures. Destruction of expired/used drug must be documented on the Drug Accountability Log and a copy of the destruction certificate kept on file in the pharmacy. Instructions for return or destruction of unused drug will be supplied at the time of expiry and at trial closure.

** 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 IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of registration 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 11.0 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.225 area of the CCTG web-site (www.ctg.queensu.ca).

Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool[2]
PATIENT ENROLLMENT FOLDER	Must be completed at time of registration to confirm eligibility.	
BASELINE REPORT	Due within 2 weeks of patient registration.	Copies of signed consent signature page(s); relevant pathology and radiology reports; ECG reports
TREATMENT REPORT	To be completed every 3 weeks (i.e. after each cycle). Due within 2 weeks of end of cycle. This form documents treatment, adverse events, investigations and response assessment for each cycle.	Relevant radiology reports.
HEALTH UTILITIES INDEX (EQ-5D)	To be completed within 7 days prior to registration and at each 12 weekly visit until progression OR maximum 1 year from registration	Relevant radiology reports.
RESOURCE UTILIZATION ASSESSMENT	To be completed at each 12 weekly visit until progression OR maximum 1 year from registration.	Relevant radiology reports.
END OF TREATMENT REPORT	To be completed when patient goes off protocol treatment. Due within 2 weeks of end of protocol treatment.	
4 WEEK POST TREATMENT REPORT	To be completed once on all patients, 4 weeks after going off protocol treatment. Due within 2 weeks after contact with patient.	
FOLLOW-UP REPORT	Continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies). For patients who go off protocol therapy before progression is documented or have objective CR, PR or SD ongoing, follow-up and a Follow-up Report will be required every 3 months for a maximum of 1 year. Due within 2 weeks after contact with patient.	Relevant radiology reports.
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
DEATH REPORT	Required for all patients[1]. Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT REPORT FORM	All reportable serious adverse events must be reported as described in Section 11.0. All reportable serious adverse events must be reported as described in Section 11.0. Preliminary CCTG Serious Adverse Event Report due within 24 hours. Updated CCTG Serious Adverse Event Report due within 7 days.	All relevant test reports; admission, discharge summaries/notes.

1 It is the investigator's responsibility to investigate and report the date/cause of death of any patient. Any death that is *thought to be treatment related* must also be reported as a Serious Adverse Event as described in section 11.

2 Supporting documents should be submitted using the Supporting Document Upload Tool. For instructions on this tool, see Power Point Presentation available on the IND.225 webpage.

APPENDIX V - 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 VI - CT FOR TEXTURE ANALYSIS

CT for Texture Analysis (Baseline, 4 weeks, 12 weeks then every 12 weeks)

CT Platform: CT exam should be performed on the same multi-slice CT scanner model within the same institution.

Intravenous contrast: Patients must undergo CT with intravenous contrast unless there is a contrast allergy that has developed after the baseline scan, in which case, the subsequent scans will be performed without intravenous contrast.

Coverage: Chest, abdomen and pelvis

Scan parameters for baseline, 4 weeks, 12 weeks then every 12 weeks:

Coverage:

1. Arterial and portal phase abdomen as per local protocol
2. Pelvis post contrast
3. Chest post contrast

Contrast: Administered as per local protocol with a single bolus

Other Parameters:

Slice thickness: 5 mm, reconstruction 2.5 mm

CT Radiation Dose and Dose Reduction Method:
If the CT scanner utilized has dose reduction capabilities (i.e. Auto-mA) these should be set for minimal dose reduction to help minimize noise related artifacts. Radiation dose saving approaches which may be in use such as those for renal colic or young adults or pediatric patients should not be used.

Central Review
All CT scans performed on trial at baseline, 4 weeks, 12 weeks then every 12 weeks should be saved to DVD/CD and sent for central review with an imaging CT form (posted on the IND 225 webpage) to:

Masoom Haider, MD
Sunnybrook Health Sciences Centre
Dept. of Medical Imaging AG-46
2075 Bayview Ave
Toronto, Ontario M4N 3M5

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.225 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 (for this study, at each 12 weekly visit until progression OR maximum 1 year from registration)

   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, eg: psychological distress, social disruption, symptoms, side effects, et cetera.

   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)

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.

LIST OF CONTACTS

PATIENT REGISTRATION

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

	Contact	Tel. #	Fax #
STUDY SUPPLIES Data Management Guidebook, Protocol, Safety Information, Electronic Case Report Forms, Available on CCTG Website	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Linda Hagerman Study Coordinator. CCTG Email: lhagerman@ctg.queensu.ca or: Dr. Janet Dancey Senior Investigator, CCTG Investigational New Drug Program Email: jdancey@ctg.queensu.ca	613-533-6430	613-533-2411
STUDY CHAIR	Dr. Teresa Petrella Study Chair Email: teresa.petrella@sunnybrook.ca	416-480-5248	416-480-7802
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Janet Dancey Senior Investigator, CCTG Investigational New Drug Program or Linda Hagerman Study Coordinator, CCTG	613-533-6430	613-533-2411
DRUG ORDERING	See Appendix III for full details.		