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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II STUDY OF DURVALUMAB AND TREMELIMUMAB IN PATIENTS WITH ADVANCED RARE TUMOURS

CCTG Protocol Number: **IND.228**

STUDY CHAIR: Abha Gupta

PATHOLOGY CO-CHAIR: Torsten Nielsen

GENOMICS CO-CHAIR: Ming Tsao

SENIOR INVESTIGATOR: Janet Dancey

BIOSTATISTICIAN: Dongsheng Tu

STUDY COORDINATOR: Joana Sederias

REGULATORY SPONSOR: CCTG

SUPPORTED BY: AstraZeneca

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

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol and any supplementary information that may be added to this document, contains information that is confidential and proprietary and must be kept in confidence.

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, in accordance with any modifications that may occur over the duration of the study, 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 AstraZeneca 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 AstraZeneca and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to AstraZeneca and CCTG of any such disclosure.

I understand that I may terminate or suspend enrollment 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 AstraZeneca with or without cause.

_____ _____

Qualified Investigator
(printed name and signature)

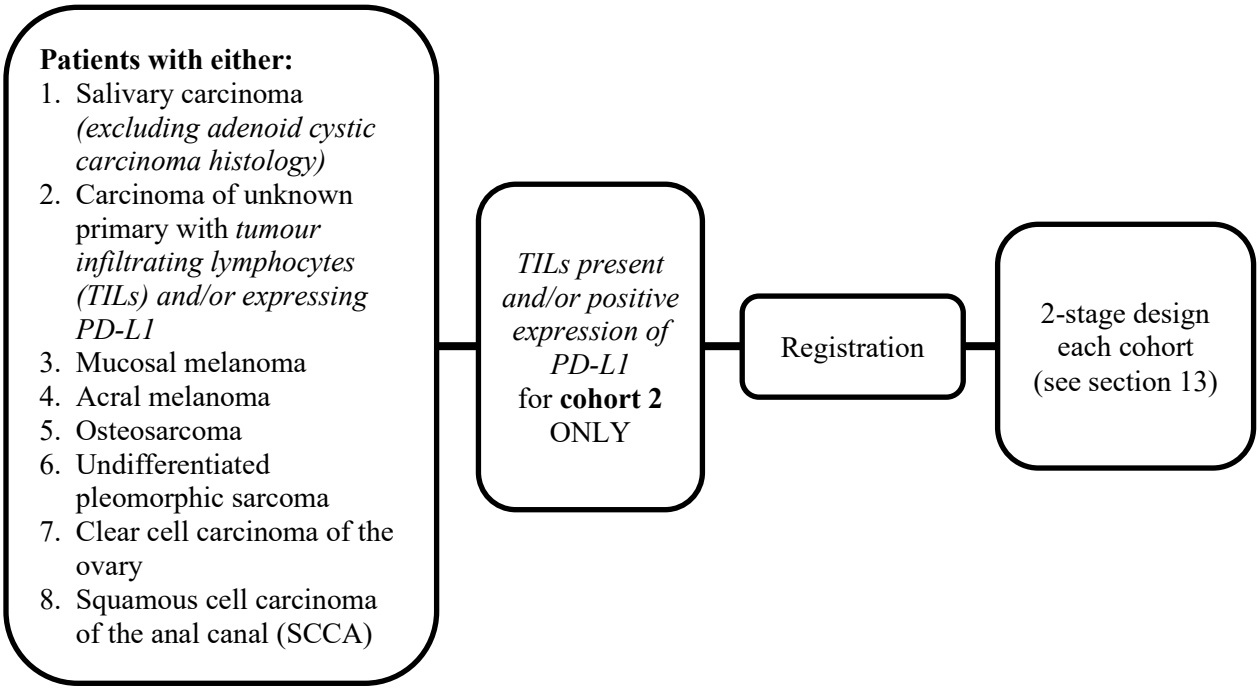
Date

Protocol Number: CCTG IND.228

CENTRE: _____

TREATMENT SCHEMA

This is a multi-centre, non-blinded, open-label single arm phase II study of durvalumab in combination with tremelimumab in patients with rare tumours. A minimum of 80, and a maximum of 160 patients will be enrolled.



1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the objective response rate of the combination of durvalumab and tremelimumab given by IV every 4 weeks for 4 cycles, followed by durvalumab alone in patients with rare tumours.

1.2 Secondary Objectives

- To evaluate the tolerability and safety of durvalumab and tremelimumab combination.
- To evaluate the effect of durvalumab and tremelimumab combination including time to progression, progression free survival and response duration.

1.3 Exploratory Objectives

- To explore the correlation between anti-tumour activity and PD-L1 expression, presence of tumour infiltrating lymphocytes (TILs) and T cell subsets within the tumour.
- To explore the correlation between anti-tumour activity and genomic alterations in tumour.
- To assess the consistency of histopathological diagnosis of rare tumours through central review of pathology specimens.
- To explore the correlation between anti-tumour activity and toxicity with blood based biomarkers.

2.0 BACKGROUND INFORMATION AND RATIONALE

Very rare cancers are poorly understood, misdiagnosed and under researched. As a result, patients with very rare cancers usually have few treatment options. The United States Congress Orphan Drug Act 1983 defines “rare” as affecting under 200,000 people in the USA, or more than 200,000 people but no reasonable expectation that the costs of developing a new drug for this condition will be recovered from its sales. This definition was created in relation to drug development and is now being used by information services, database, and registry organizers. An extension of this definition to Canada, with roughly one-tenth the US population, would be < 20,000 people. Cancers like leukemia, head and neck cancer fall within this definition. However, considerably greater challenges, in terms of research, funding, and available information exist for ‘very rare’ cancers. Unlike the latter tumour types, even small phase II clinical trials for patients with very rare tumours are difficult to conduct. The ethical, regulatory and resource demands of maintaining a trial at a centre that will accrue few or no patients per year are disincentives to mounting multi-centre treatment trials. A more relevant definition of rare disease may be that of the European Commission on Public Health which defines rare diseases as "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them”.

Compelling medical and scientific reasons exist for mounting multicentre treatment clinical trials in very rare tumours. Options for patients with such cancers are limited. Due to their infrequency, diagnosis may be difficult and delayed, therapeutic studies are most often retrospective case series of patients treated over a period of years. In addition to the unmet medical need, there is a compelling research need to investigate these tumours. Although basic and translational research is limited, some rare tumours appear to be more biologically homogenous and have potentially identifiable oncogenic drivers than more common tumours. While the logistics of mounting phase II trials in rare tumours seem initially daunting, with relatively few treatment options and few competing trials, recruitment to trials may be more easily accomplished than in more common disease settings, assuming challenges of running a trial with anticipated limited enrolment at individual institutions are addressed. Finally, determining efficient means of conducting trials in rare tumours defined histologically may inform the design and conduct of trials of rare tumour populations based on molecular profiles required to evaluate personalized medicine approaches and facilitate the evaluation of individualized therapies.

To address the challenges of conducting trials of novel therapies for patients with very rare cancers, we designed and successfully completed IND.206, a multi-arm, multiphase study of sunitinib and temsirolimus in patients with rare cancers (defined as <100 eligible patients/year). There were 10 histologic or genetic defined rare tumour cohorts and 1 exploratory cohort testing both of the agents separately. Over three years, 136 patients were enrolled, and 162 patients were registered (25 patients were registered and received both agents). Activity was seen in multiple cohorts *[Dancey 2015]*. The majority of participating sites were able to enroll multiple patients on the study, suggesting that the design is feasible and an acceptable means of testing promising agents in very rare cancer settings.

2.1. Immunotherapy & Immune Checkpoint Inhibitors

Programmed death 1 (PD-1) protein is a co-inhibitory receptor known to be expressed on activated T cells, which when bound to its ligand PD-L1, limits T cell antitumour activity in the tumour microenvironment *[Fife 2008]*. Blockade of PD-1 engagement with its ligand PD-L1, induces immune responses in vitro and has been shown to mediate preclinical activity *[Fife 2009]*. Clinically, blockade of the PD-1 inhibitory checkpoint pathway by inhibiting PD-1/PD-L1 engagement, has been shown to induce tumour regression across many cancer types, including melanoma, renal cell, colon, lung and bladder cancers *[Pardoll 2012; Brahmer 2012]*. Single agent immunotherapy with anti-PD-1 or anti-PD-L1 antibodies across many tumour types has been generally well tolerated, with common drug related adverse events mainly limited to grade 1 or 2 fatigue, diarrhea, rash, pruritus, nausea and decreased appetite. Immune-related adverse events are uncommon (<2%), and include pneumonitis, vitiligo, colitis, hepatitis and hypophysitis and thyroiditis *[Brahmer 2012; Topalian 2012; Antonia 2014]*.

CTLA-4 is another co-inhibitory receptor expressed on activated T cells and regulates early stage T cell activation, reducing the amplitude of T-cell activation. Inhibition of CTLA-4 signaling is a validated approach to cancer therapy, as shown by the approval in 2011 of ipilimumab for the treatment of patients with metastatic melanoma based on an improvement in overall survival (OS) of patients with advanced melanoma *[Hodi 2010; Robert 2011]*.

In general, tumour response rates to anti-CTLA-4 therapy are low (~10%) in melanoma. However, in patients who respond, the responses are generally durable. Because these agents activate the immune system, responses can be delayed and some patients may have perceived progression of their disease in advance of developing disease stabilization or a tumour response. In some cases, early growth of pre-existing lesions or the appearance of new lesions may have been due to immune-cell infiltration into the tumour and not due to proliferation and expansion of neoplastic cells *[Wolchok 2009]*. Although the impact on conventionally-defined median progression free survival (PFS) can be small, durable response or stable disease seen in a proportion of patients can lead to significant prolongation of PFS and OS in a subset of patients.

2.1.1. *Tremelimumab*

Tremelimumab is a human IgG2 monoclonal antibody (MAb) directed against the T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4) *[Tarhini 2013]*. Tremelimumab binds to CTLA4 and blocks the binding of the antigen-presenting cell ligands B7-1 and B7-2 to CTLA4, resulting in inhibition of B7-CTLA4-mediated downregulation of T-cell activation. In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumour activity in animal models, including killing of established murine solid tumours and induction of protective anti-tumour immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumour activity in patients with solid tumours. Tremelimumab has been evaluated as a single agent in a number of malignancies. In a large phase 3 randomized study comparing tremelimumab with dacarbazine (DTIC)/temozolomide in patients with advanced melanoma, the reported median OS in the final analysis was 12.6 months for tremelimumab versus 10.7 months for DTIC/temozolomide (HR = 1.14; p=0.13) *[Ribas 2013]*. The phase 3 study of tremelimumab in patients with metastatic melanoma did not meet the primary endpoints of improved OS. However, response duration (measured from date of random assignment) was significantly longer after tremelimumab (35.8 v 13.7 months; P = .0011). These data suggest the drug can be administered safely and that there is activity of tremelimumab in melanoma *[Kirkwood 2010; Ribas 2013]*.

2.1.2. *Durvalumab*

Durvalumab is a human MAb of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of two identical heavy chains and two identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function *[Stewart 2015; Ibrahim 2015]*.

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80 *[Stewart 2015; Ibrahim 2015]*. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. *In vivo* studies show that durvalumab inhibits tumour growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumour model when given as monotherapy and resulted in complete tumour regression in > 50% of treated mice when given in combination with chemotherapy *[Stewart 2015; Ibrahim 2015]*.

2.2. Rationale for the Combination of Durvalumab and Tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic anti-tumour activity because the mechanisms of action of CTLA-4 and PD-1 are non-redundant *[Pardoll 2012]*. The combination of nivolumab and ipilimumab to patients with advanced melanoma induced clinically and statistically significant improvement in PFS and response rate than those obtained with single-agent therapy in a randomized phase III trial *[Larkin 2015]*. The frequency of grade 3 and 4 immune related toxicity was higher but manageable. Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group. Importantly, responses appeared to be deep and durable *[Wolchok 2013]*. The higher response rate and improved survival suggests that the combination is able to induce an anti-tumour response in patients with cancers that are otherwise refractory to the individual agents.

Promising results have been observed in the recently published phase 1B study of combination durvalumab and tremelimumab in 102 patients with NSCLC *[Antonia 2016]*.

We hypothesize that one or more rare tumours will be sensitive to the combination of durvalumab and tremelimumab and sensitivity will be linked to identifiable biomarkers.

The defined cohorts and rationale for testing the agents is provided in the following table:

2.3 Rationale for Rare Cancer Cohorts

For this trial, recent scientific and clinical literature were reviewed to determine rare cancers that might rationally be expected to be sensitive to combined immune check point therapy. Currently, expression of immune markers, PD1/PDL1, immune cell infiltrate of tumour and high mutation load correlative with activity in at least some settings. In addition, early clinical trials and case reports support sensitivity of some rare cancers. The proposed tumour types, rationale and relevant references are provided in the table below. Furthermore, the trial is designed to enhance the operational efficiencies of the study by allowing the enrolment of multiple tumour histologies into separate cohorts. By including multiple rare tumour histologies, many more patients can be enrolled/site under a single protocol. The two agent combination activity can be assessed within a single common protocol and this will allow the generation of data on objective response.

	Rare Tumour Cohort	Comment/Rationale	References
1	Salivary carcinoma	Unmet medical need. SGTs are characterized by recurrent genetic alterations, particularly chromosome translocations.	*[Rettig 2016; Matthew 2015]*
2	Carcinoma of unknown primary with tumour infiltrating lymphocytes (TILs) and/or expressing PD-L1	Unmet medical need. A subset of CUPs have immune cell infiltration and may represent cancers sensitive to immunotherapies.	*[Hampig 2016]*
3	Mucosal Melanoma	Unmet medical need. Objective responses reported with nivolimab.	*[Larkin 2015; Lian 2014]*
4	Acral melanoma	Unmet medical need. Objective responses seen with ipilumumab	*[Johnson 2015]*
5	Osteosarcoma	High-grade osteosarcomas have complex chaotic karyotypes. Many immune signaling pathways are important in bone homeostasis. The success of the innate immune stimulant mifamurtide in the adjuvant treatment of non-metastatic osteosarcoma suggests that newer immune-based treatments are promising.	*[D'Angelo 2014; Kansara 2014]*
6	Undifferentiated pleomorphic sarcoma	Increased mutational load seen in these tumours may be predictive for response to immunotherapy agents	*[Lim 2015]*
7	Clear cell carcinoma of the ovary(expanded to include 20 additional patients in Jan 2019)	Objective responses were noted in a phase 1b study of avelumab, anti-PD-L1 monoclonal antibody in clear cell ovarian carcinoma, and in a phase II clinical trial in heavily-treated platinum-resistant ovarian cancer, OCCC subtypes. In addition, promising emerging preclinical and clinical data supports the further development of immune checkpoint inhibitors in gynecologic cancers.	*[Disis 2015; Oda 2018; Heong 2017]*
8	Squamous cell carcinoma of the anal canal	Seven/33 evaluable patients (21%) had a partial response to nivolimab	*[Morris 2016]*

Rationale for the Expansion of the Clear Cell Ovarian Cohort:

The clear cell carcinoma of the ovary cohort (#7) met its accrual goal of 20 patients in April of 2018. Efficacy analysis showed objective responses in 7/19 patients, an overall response rate of > 30%. The combination was tolerable and toxicity profile was as expected for combined immune checkpoint inhibitors. Durvalumab/tremelimumab related events are mostly grade 1-2 with most common ones being fatigue, rash, diarrhea and hypothyroidism. Grade 3 related events reported as an SAE in this cohort were: auto-immune hepatitis in 2 pts, increased lipase (without pancreatitis), AA-amyloidosis, renal failure, colitis and rash. The majority of hematologic and biochemical events are grade 1-2, however anemia grade 3 was seen in 3 patients.

Given the activity seen and with new literature showing that OCCC both tumour cells and tumour microenvironment may be associated with sensitivity to immune checkpoint inhibitors *[Oda 2018]*, the cohort will be expanded an additional 20 more patients.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Durvalumab

3.1.1 *Name and Chemical Information*

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand (PD-L1) (B7 homolog 1[B7-H1], cluster of differentiation [CD]274 to programmed cell death 1 (PD-1; CD279) and CD80 (B7).

See the current durvalumab Investigator Brochure for additional details and the most up to date information.

3.1.2 *Chemical Structure*

Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C 1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

3.1.3 *Mechanism of Action*

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ).

3.1.4 *Experimental Antitumour Activity*

- In a xenograft model durvalumab inhibited human tumour growth via a T-cell-dependent mechanism.
- An anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumour model when given as monotherapy and resulted in complete tumour regression in > 50% of treated mice when given in combination with chemotherapy.
- Combination therapy (dual targeting of PD-L1 and CTLA-4) resulted in tumour regression in a mouse model of colorectal cancer.
- Dual targeting of PD-1 and PD-L1 in a syngeneic model of sarcoma in mice demonstrated statistically significant mean tumour growth delay relative to the control group.

3.1.5 *Animal Toxicology*

In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab-related adverse effects that were considered to be of relevance to humans.

Data from the pivotal 3-month GLP toxicity study with durvalumab in cynomolgus monkeys showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

3.1.6 *Clinical Trials*

As of the most recent Investigator's Brochure, over 12,000 subjects have been enrolled and treated in ongoing durvalumab clinical studies. No studies have been completed or terminated prematurely due to toxicity.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents appears consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumour types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include pneumonitis, hepatitis, diarrhea/colitis and intestinal perforation, endocrinopathies (thyroiditis, hypo and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism diabetes insipidus and Type 1 diabetes mellitus), nephritis, rash/dermatitis, pancreatitis, myocarditis, myositis/polymyositis and rare/less frequent irAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome. Other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, cholangitis sclerosing, cystitis, uveitis and other events involving the eye (e.g. keratitis and optic neuritis), skin (e.g. scleroderma, vitiligo and pemphigoid), hematological (e.g. hemolytic anemia, immune-mediated neutropenia and immune thrombocytopenic purpura) and rheumatological (e.g. polymyalgia rheumatic and autoimmune arthritis) events, vasculitis, non infectious encephalitis or non infectious meningitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs. Please refer to the most recent version of the Investigator Brochure for incidence.

3.1.7 *Pharmaceutical Data - Durvalumab*

Supplied:
Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-HCI, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0.

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

Route of Administration:
Intravenous.

Please refer to the IND.228 Pharmacy Manual for additional details.

3.2 Tremelimumab

3.2.1 *Name and Chemical Information*

Tremelimumab is a human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass that inhibits binding of B7 ligands (B7.1 (CD80) or B7.2 (CD86)) to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; cluster of differentiation [CD]152).

See the current tremelimumab Investigator Brochure for additional details and the most up to date information.

3.2.2 *Chemical Structure*

Tremelimumab has an overall molecular weight of approximately 149 kDa including oligosaccharides.

3.2.3 *Mechanism of Action*

Tremelimumab binds with high affinity and specificity to human CTLA-4, a cell surface receptor expressed primarily on activated T cells. Binding of CTLA-4 to its target ligands (B7.1 and B7.2) on antigen-presenting cells, provides a negative regulatory signal, which limits T-cell activation. Tremelimumab blocks this interaction of B7 ligands with CTLA-4, thus leading to prolongation and enhancement of T-cell activation and expansion. This mechanism is supported by in vitro studies where tremelimumab antagonizes binding of CTLA-4 to B7 ligands and enhances human T-cell activation as demonstrated by increased cytokine (IL-2, IFN-γ) production.

3.2.4 *Experimental Antitumour Activity*

- In a mouse model of fibrosarcoma, an anti-mouse CTLA-4 antibody demonstrated dose-dependent antitumour activity and, at the maximum dose tested, resulted in complete tumour regression in 4 of 5 treated animals. Also these animals were resistant to tumour rechallenge, demonstrating a durable antitumour immunity. Finding was corroborated in other mouse models of cancer.
- In a mouse model of colon cancer, the combination of anti-mouse PD-L1 and anti-mouse CTLA-4 resulted in greatly increased activity with tumour regression observed in all mice treated relative to control.

3.2.5 *Clinical Trials*

To date, 34 clinical studies have been conducted in over 1500 patients in both monotherapy and combination therapy clinical trials. Full details are described in the current tremelimumab investigator brochure.

To date, no tumour type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to subjects with melanoma). Treatment-related AEs were reported at similar rates in the 10 and 15 mg/kg groups, and were mostly Grade 1 or 2 in severity. The most frequent (in > 5% of subjects) treatment-related AEs (all grades) in patients with tremelimumab monotherapy were diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, headache, pyrexia, abdominal pain, and colitis. Please refer to the most recent version of the Investigator Brochure for incidence.

Across clinical trials, a pattern of efficacy has emerged that is similar to the anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumour types. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting several months even in subjects with aggressive tumours such as refractory metastatic melanoma.

3.2.6 *Pharmaceutical Data - Tremelimumab*

Supplied:
Supplied as a vialed solution containing 400 mg (nominal) tremelimumab. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine-HCI, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, 0.27 mM disodium edetate dehydrate (EDTA), pH 5.5.

Storage:
Tremelimumab must be stored at 2°C to 8°C and must not be frozen. The product should be protected from light when not in use.

Route of Administration:
Intravenous.

Please refer to the IND.228 Pharmacy Manual for additional details.

3.3 Fixed Dosing in Durvalumab and Tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumours). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) *[Wang 2014]*. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others *[Ng 2006, Wang 2009, Zhang 2012, Narwal 2013]*. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic / pharmacodynamics parameters *[Zhang 2012]*.

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Based on average body WT of 75 kg, a fixed dose of 1500mg Q4W and 75 mg tremelimumab (equivalent to 1 mg/kg) is planned.

Fixed dosing of durvalumab and tremelimumab is recommended only for subjects with > 30 kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule.

4.0 STUDY POPULATION

The trial population will consist of patients with advanced (metastatic or locally advanced) histologically confirmed rare cancers as defined in section 4.1.1 that is unresectable and for which no curable therapy exist.

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

4.1 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:

4.1.1 Patients must have histologically and/or cytologically confirmed cancer that is advanced / metastatic / recurrent or unresectable and for which no curative therapy exists as follows:

1. Salivary carcinoma (excluding adenoid cystic carcinoma histology)
2. Carcinoma of unknown primary with tumour infiltrating lymphocytes (TILs) and/or expressing PD-L1
3. Mucosal melanoma
4. Acral melanoma
5. Osteosarcoma
6. Undifferentiated pleomorphic sarcoma
7. Clear cell carcinoma of the ovary
8. Squamous cell carcinoma of the anal canal (SCCA)

4.1.2 All patients must have a tumour tissue from their primary or metastatic tumour available (See Section 11.2 for slide specifications, as well as section 12.1).

4.1.3 Presence of clinically and/or radiologically documented disease. All radiology studies must be performed within 28 days prior to registration (within 35 days if negative).

All patients must have at least one measurable lesion as defined by RECIST 1.1 that has not been the site of the protocol mandated biopsy. The criteria for defining measurable disease are as follows:

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

4.1.4 Patients must be ≥ 16 years of age.

4.1.5 Patients must have an ECOG performance status of 0 or 1.

4.1.6 *Previous Therapy*

Cytotoxic Chemotherapy:
Patients may have received prior chemotherapy – no limit on number of prior regimens.

Other Systemic Therapy:
Patients may have received other prior therapies including, angiogenesis inhibitors, PARP inhibitors or signal transduction inhibitors (tyrosine kinase inhibitors). Prior therapy with PD-1/PD-L1 or CTLA-4 inhibitors is not allowed.

Patients must have recovered from all reversible toxicity related to prior chemotherapy or systemic therapy (unless grade 1, irreversible, or considered by investigator as not clinically significant) and have adequate washout as follows:

Longest of one of the following:

- Two weeks
- 5 half-lives for investigational agents
- Standard cycle length of standard therapies

Radiation:
Prior external beam radiation is permitted provided a minimum of 28 days (4 weeks) have elapsed between the last dose of radiation and date of registration. Exceptions may be made for low-dose, non-myelosuppressive radiotherapy after consultation with CCTG senior investigator. Concurrent radiotherapy is not permitted. Patients planned for concurrent chemotherapy-radiation are not eligible.

Surgery:
Previous surgery is permitted provided that a minimum of 28 days (4 weeks) have elapsed between any major surgery and date of registration, and that wound healing has occurred.

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

Hematology	Absolute neutrophils	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
	Hemoglobin	≥ 90 g/L
Chemistry	Bilirubin	≤ 1.5 x ULN (upper limit of normal)*
	AST and ALT	≤ 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
	Serum creatinine *or:* Creatinine clearance**	< 1.25 x ULN ≥ 40 mLs/min

* If confirmed Gilbert's, eligible providing ≤ 3 x ULN.
** Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft and Gault equation below:

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

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

4.1.8 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to registration in the trial and prior to tests which are considered to be study specific (see Section 5.0) to document their willingness to participate.

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

4.1.9 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.

Female patients of childbearing potential who are sexually active with a non sterilized male partner must use at least one highly effective method of contraception while on study and for 6 months after the last dose of durvalumab and tremelimumab or for 3 months after the last dose of durvalumab alone. Male partners of a female subject and non-sterilized male patients who are sexually active with a female partner of childbearing potential must use male condom plus spermicide while on study and for 6 months after the last dose of durvalumab and tremelimumab or for 3 months after the last dose of durvalumab alone. Female partners of a male subject must use a highly effective method of contraception throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. See Section 9.3.1 for additional details.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin 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.

Male patients should also refrain from donating sperm during the study and for 6 months after the last dose of durvalumab and tremelimumab or for 3 months after the last dose of durvalumab alone.

4.1.10 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 at 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, response assessment, adverse events, and follow-up.

4.1.11 Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab or tremelimumab.

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

4.2 Ineligibility Criteria

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

4.2.1 Patients with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other cancers curatively treated with no evidence of disease for ≥ 5 years.

4.2.2 Active or prior documented autoimmune or inflammatory disorders including inflammatory bowel disease (e.g. colitis or Crohn's disease), diverticulitis with the exception of diverticulosis, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), rheumatoid arthritis, hypophysitis, uveitis, etc., within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:

- Patients with alopecia.
- Patients with Grave's disease, vitiligo or psoriasis not requiring systemic treatment (within the last 2 years).

- Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement.

4.2.3 History of primary immunodeficiency, history of allogenic organ transplant that requires therapeutic immunosuppression and the use of immunosuppressive agents within 28 days of registration*

* *NOTE: Intranasal/inhaled corticosteroids or systemic steroids that do not to exceed 10 mg/day of prednisone or equivalent dose of an alternative corticosteroid are permissible.*

4.2.4 Live attenuated vaccination administered within 30 days prior to registration.

4.2.5 History of hypersensitivity to durvalumab or tremelimumab or any excipient. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA4, including tremelimumab.

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

4.2.7 Untreated symptomatic brain metastases or brain metastases in whom radiation or surgery is indicated.

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

4.2.9 Patients with serious illnesses or medical conditions which would not permit the patient to be managed according to the protocol (including corticosteroid administration), or would put the patient at risk. This includes but is not limited to:

- History of significant neurologic or psychiatric disorder which would impair the ability to obtain consent or limit compliance with study requirements.
- Active infection requiring systemic therapy; (including any patient known to have active hepatitis B, hepatitis C or human immunodeficiency virus (HIV) or tuberculosis or any infection requiring systemic therapy).
- Active peptic ulcer disease or gastritis.
- Known pneumonitis or pulmonary fibrosis with clinically significant impairment of pulmonary function.

4.2.10 Pregnant or lactating women.

Men and women of child-bearing potential must agree to use adequate contraception as described in Section 4.1.9.

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

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

Required Investigations	Pre-study (≤ 7 days prior to registration)	Day 1 each cycle, and as clinically indicated	Day 1 every 12 weeks	4 weeks after completion of protocol therapy	3 month follow-up (only required for pts without confirmed PD and ongoing toxicities [1])
History and Physical Exam					
Including: height and weight, ECOG performance status, documentation of all measurable and non-measurable disease, clinical tumour measurements (if applicable); Vital signs[2]: blood pressure, heart rate, temperature	X	X		X	
Laboratory Procedures/Assessments[3]					
CBC, neutrophils, lymphocytes , platelets	X	X		X[4]	X[4]
PTT, PT/INR (if on anticoagulants)	X	X		X[4]	X[4]
Serum creatinine, creatinine clearance (calculated), electrolytes (calcium, potassium, magnesium) bilirubin, ALP, AST, ALT, LDH, albumin, glucose, amylase[5], lipase[5], TSH[6]	X	X		X[4]	X[4]
Pregnancy Test[7]	X	X[8]			
Radiology					
Tumour Imaging (Chest, abdomen and pelvis scan; other scans as necessary to document disease) Bone scan for osteosarcoma patients	within 28 days prior to registration or 35 if negative		X[9]	X[10]	X[10]
Other Investigations					
Tumour markers (i.e. CA-125, etc.) [11] if applicable	X	as clinically indicated			
LVEF[12]	(within 28 days prior to registration)				
Urinalysis (*dipstick – including protein, specific gravity, glucose and blood)*	X				
Archival Tumour Tissue for assessment of TILs and PD-L1 expression (*pre-screening – cohort #2 only)*	X[13]				
Correlative Studies Blood Collection	X[14]	See Section 12.0 for details			
Adverse events	X	Continuously		X[1]	

footnotes on next page ...

1	Every three months thereafter to follow adverse events felt related until resolved to ≤ Grade 2. Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) (see Appendix V).
2	Patients will be monitored before, during and after the first cycle infusion of tremelimumab and durvalumab with assessment of vital signs to be collected ≤ 30 minutes prior to start of infusion then every 30 ±5 minutes during infusion; a 1-hour observation period is recommended after the tremelimumab. Assessment of vital signs in subsequent cycles is required prior to the start of the infusion, and then as clinically indicated. If no clinically significant infusion reactions are observed during or after the first cycle of tremelimumab+durvalumab therapy, subsequent infusion observation periods can be at the investigator's discretion.
3	Pre-treatment blood draws and physical exams may be done one working day prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol. If a patient shows an AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, refer to Appendix II for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.
4	Required at 4 weeks. To be done additionally every 3 months thereafter to follow abnormal lab results felt related until resolved to ≤ Grade 2.
5	It is preferable that both amylase and lipase are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.
6	Free T3 and free T4 will be measured if TSH is abnormal.
7	For women of childbearing potential only (urine or serum test). Within 72 hours prior to registration. Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.
8	As clinically indicated in WOCBP
9	To ensure comparability, baseline scans and subsequent scans to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Maintain schedule every 12 weeks even if cycles are delayed. For osteosarcoma patients, every 3 months if bone mets are present at baseline. For patients remaining on study beyond January 2022, the frequency of imaging assessment may be reduced to every 6 months at the description of the investigator and discussion with CCTG.
10	To be done every 12 weeks until relapse or progression (iCPD) for up to 2 years, for patients with CR/iCR, PR/iPR, SD/iSD response as defined in Section 8. Patients with CR/iCR or PR/iPR or equivocal PD (pseudoprogression)/iUPD should have scans repeated after 4 weeks, but no more than 8 weeks, to confirm response.
11	Depending on histology, applicable markers (i.e. CA-125 for the Clear Cell Carcinoma of the Ovary cohort) must be reported as per standard of care at local sites.
12	Only if significant cardiac history (see section 4.2.6).
13	Must be confirmed available prior to registration on ALL patients. Archival tissue submission should be sent at the same time that the baseline CRF is submitted for each patient. Prescreening of TIL and PDL1 expression is required for cohort 2 patients prior registration. See Section 12.0 for details.
14	After registration but before the first dose of study treatment. See lab manual for details.

5.1 Follow-up for Ineligible or Patients That Go Off Study Prior to Starting Protocol Therapy

The follow-up requirements for ineligible patients/patients who have received no protocol therapy prior to going off study include submission of the Baseline Report plus an End of Treatment Report. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

6.0 ENTRY/REGISTRATION PROCEDURES

6.1 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 are also available in the "EDC Data Management Guidebook", posted on the IND.228 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients please contact the help desk (link in EDC) or the IND.228 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.228)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values

6.2 Registration

Registration 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 registered patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients are outlined in Section 5.1.

The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report only. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

7.0 TREATMENT PLAN

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

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

7.1 Durvalumab and Tremelimumab Treatment Plan

7.1.1 *Drug Administration*

When durvalumab is given with tremelimumab, tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion.

One cycle will be defined as 4 weeks. Tremelimumab will only be given for the first 4 cycles.

Agent(s)	Dose	Route	Duration	Schedule
Durvalumab	1500 mg	IV	60 min	Day 1 every 4 weeks
Tremelimumab	75 mg	IV	60 min	Day 1, cycles 1-4
Patients with a body weight of less than or equal to 30kg should be dosed using a weight based dosing schedule. See Section 3.3.				

7.1.2 *Premedication*

No routine premedication (e.g. for nausea) or prophylaxis for hypersensitivity is required. Management of symptoms should take place as necessary (See Appendix II). Premedication is not expected to be required. See Appendix II with respect to premedication of patients that have had a prior ≤ Grade 2 infusion-related reaction. Details of any premedication or concomitant medication given to manage or prevent adverse events should be recorded on the electronic case report form (eCRF).

7.1.3 *Patient Monitoring*

Patients will be monitored before, during infusion and after the infusion of tremelimumab and durvalumab with assessment of vital signs as specified in Section 5.0. A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Guidelines for management of infusion-related reaction are summarized in Appendix II.

All patients should be closely monitored according to guidelines in Section 5.0 and be advised to contact the treating centre in the case of significant toxicities.

7.1.4 *Dose Modifications*

The major toxic effects of durvalumab or tremelimumab which are anticipated to limit dosing are hypersensitivity/ infusion related reactions and possible class related immune related AEs, based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation. Potential immune related AEs include pneumonitis, hepatitis, diarrhea/colitis and intestinal perforation, endocrinopathies (thyroiditis, hypo and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism diabetes insipidus and Type 1 diabetes mellitus), nephritis, rash/dermatitis, pancreatitis, myocarditis, myositis/polymyositis and rare/less frequent irAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome. Other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, cholangitis sclerosing, cystitis, uveitis and other events involving the eye (e.g. keratitis and optic neuritis), skin (e.g. scleroderma, vitiligo and pemphigoid), hematological (e.g. hemolytic anemia, immune-mediated neutropenia and immune thrombocytopenic purpura) and rheumatological (e.g. polymyalgia rheumatic and autoimmune arthritis) events, vasculitis, non infectious encephalitis or non infectious meningitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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

Dose adjustments (slowing/interruption of infusion rate, omission of a dose, or permanent discontinuation) will be made for hematologic and other adverse events**.**

If the infusion cannot be administered, it should be omitted until the next planned infusion.

The next cycle should not be given until the laboratory criteria in Section 4.1.7 are met and resolution of all drug related toxicity to ≤ grade 2. Discuss with CCTG if asymptomatic/not felt to be clinically significant.

7.1.5 *Management of Toxicity*

Please refer to detailed toxicity management guidelines in Appendix II.

All dose modifications should be documented with clear reasoning and documentation of the approach taken.

7.1.6 *Management of Infusion Reactions*

Guidelines for management of infusion-related reaction are summarized in Appendix II. The standard infusion times for both durvalumab and tremelimumab are 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to appropriate drugs and medical equipment to treat acute anaphylactic reactions, emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

7.1.7 *Dose Adjustments for Immune Related Adverse Events and Other (Non-Immune Related) Adverse Events Related to Study Therapy*

Guidelines for dose modification and toxicity management of immune related and non-immune related adverse events are summarized in Appendix II.

Centres must contact CCTG in the event of severe event(s), especially when the use of drugs such as infliximab are considered.

7.2 Duration of Therapy

Treatment with durvalumab ± tremelimumab (to a maximum of 4 doses, cycles 1-4) will continue until disease progression or unacceptable toxicity.

Exceptions to the duration of treatment for patients with continued response may be made after consultation with CCTG.

7.3 Patient Compliance

Treatment compliance will be monitored by drug accountability, as well as recording drug administration in the patient's medical record and case report form (CRF).

7.4 Concomitant Therapy

Details of any concomitant medications (prescription, non-prescription, or over-the-counter medications) taken by the patient at study entry and during protocol therapy must be recorded on the appropriate electronic case report forms (eCRFs).

7.4.1 *Permitted*

- Growth factors may be used according to centre policy to treat life threatening toxicity but cannot be used in place of protocol defined dose adjustments. Please consult CCTG senior investigator in the case of patients experiencing multiple delays as exceptions may be made for patients who are benefitting from protocol therapy.
- Other supportive and palliative care (e.g. pain control) as required throughout the study.
- Anti-emetics or anti-diarrheal agents as required.

7.4.2 *Not Permitted*

- Cytokines;
- Other anti-cancer treatment;
- Other investigational therapy;
- Concurrent radiation treatment; (Note: if patients require palliative radiation or prophylactic radiation (e.g. of brain) consult CCTG for exception to this rule; protocol therapy will need to be held prior to and during the radiation).
- Corticosteroids IV or PO (except for the treatment of ≥ grade 3 infusion reaction, treatment-related toxicity (See Appendix II), and nausea prophylaxis for chemotherapy). Note: Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed. Patients who are on low oral doses of prednisone (5 mg BID or dexamethasone equivalent) must discontinue prior to study entry unless medically contraindicated.
- Live attenuated vaccines within 30 days of durvalumab dosing (i.e. 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Adverse Events*

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

8.1.2 *Evaluable for Response*

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

Response and progression will be evaluated in this study using 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 2017]*. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

8.2 Response and Evaluation Endpoints

Response and progression 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 Immune-Related modified RECIST. Investigators should continue treatment, as appropriate, in the absence of unacceptable toxicity, until unequivocal disease progression. This is particularly important for patients in whom pseudoprogression may have occurred. Follow up response assessments must be continued until unequivocal disease progression has occurred.

8.2.1 *Measurable Disease*

Measurable tumour lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 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.

8.2.2 *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.

8.2.3 *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 8.2.4). 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.

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

8.2.4 *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”.

8.2.5 *Response*.

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

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

Complete Response (CR): disappearance of *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [ref RECIST 1.1]) 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. Patients with CR/iCR or PR/iPR should have scans repeated after 4 weeks, but no more than 8 weeks, to confirm response.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden appears to have increased by at least 73% in volume or, in select instances where tumour burden has increased sufficiently to require urgent medical intervention (e.g. radiation for spinal cord compression or drainage of a fluid collection. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Patients that are clinically well may continue on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of PD by immune response criteria *[Seymour 2017]*. In this situation, patients do not have unequivocal progression until immune response criteria are met (see Table 4 below).

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

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

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

* Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see table 5.

8.3 Immune-Related Response Assessment

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

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

Confirming Progression

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

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

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

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

New Lesions

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

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

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

Table 4: Time-point (TP) iResponse

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

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

Table 5: iRECIST Best Overall Response (iBOR)

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

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

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

8.4 Response Duration (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).

8.5 Stable Disease Duration

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

8.6 Methods of Measurement

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

8.6.1 *Clinical Lesions*

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

8.6.2 *Chest X-ray*

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

8.6.3 *CT, MRI*

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual cases.

8.6.4 *Ultrasound*

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

8.6.5 *Endoscopy, Laparoscopy*

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

8.6.6 *Tumour Markers*

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

8.6.7 *Cytology, Histology*

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

9.0 SERIOUS ADVERSE EVENT REPORTING

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

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

9.1 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 serious adverse event occurring after this 30-day period which is related to protocol treatment must also be reported in an expedited manner (see Section 9.2 for reporting instructions).
- 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
- Adverse events that are suspect to be immune mediated AND that require intervention with high doses of steroids are considered to be medically important events that require intervention to prevent a fatal, life-threatening or hospitalization event. They should be reported as expedited events using the SAEs reporting system.
- In addition, if a patient shows an AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, refer to Appendix II for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

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.

9.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the IND.228 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

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

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

FAX paper SAE Report to:

IND.228 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.228 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

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

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of childbearing potential (WOCBP) and men who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criteria 4.1.9. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

A highly effective method of contraception is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Highly effective methods of contraception are described in the table below. Note that some contraception methods are **not** considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Highly Effective* Methods of Contraception	
Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (e.g. Mirena®)**	• Etonogestrel implants: e.g. Implanon or Norplan • Intravaginal device: e.g. ethinylestradiol and etonogestrel • Medroxyprogesterone injection: e.g. Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)
* Highly effective (i.e. failure rate of <1% per year). ** This is also considered a hormonal method.	

9.3.2 *Pregnancy Reporting*

If a patient becomes pregnant during the course of the study, the investigational agent should be discontinued immediately.

Pregnancy itself - occurring in female participants, and female partners of male participants - is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

The investigator is required to report to CCTG any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 6 months after the last dose 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, spontaneous miscarriage; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

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).

9.5 CCTG Reporting Responsibility to AstraZeneca

AstraZeneca will be notified of all protocol reportable serious adverse events (as defined in Section 9.1) within one working day of receipt of report at CCTG. CCTG, as sponsor, will determine regulatory reportability in Canada. AstraZeneca will be notified of all pregnancies and outcomes of pregnancies within 30 days of receipt of the report at CCTG.

9.6 CCTG and AstraZeneca Reporting Responsibilities

AstraZeneca will report all regulatory reportable serious adverse events from non-CCTG trials (Safety Updates) with durvalumab and tremelimumab 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.228 investigators. AstraZeneca will report these events to Health Canada.

9.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities 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.228 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.228 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.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients who are clinically stable but meet the criteria for iUPD should be continued on treatment until the next disease assessment at least 4 weeks later. It is recommended that the next imaging assessment be no longer than 8 weeks later in order to ensure patients remain fit for salvage therapies. Clinical stability is defined as:

- Stability or improvement in performance status.
- No clinically relevant increase in disease related symptoms such as pain or dyspnea (generally understood to mean a requirement for increased palliative intervention as below).
- No requirement for increased management of disease related symptoms including increased analgesia, radiation or other palliative care.

Patients may stop protocol treatment (durvalumab ± tremelimumab) 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 7.0.
- Tumour progression or disease recurrence as defined in Section 8.0; note: investigators are encouraged to continue treatment if pseudoprogression is suspected or mixed responses are seen *[Wolchok 2009]*.
- Request by the patient.
- Completion of therapy as outlined in Section 10.2. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Duration of Protocol Treatment

(see Section 8.0 for response definition)

- For complete responders, therapy will continue until progression (refer to Section 7.2).
- For partial responders, therapy will continue until progression. For stable patients, therapy will continue until progression (refer to Section 7.2).
- Patients who progress (treatment failure) will stop all treatment and go off study at the time unequivocal progression is documented clinically and/or radiographically.

10.3 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

10.4 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. Thereafter, continued follow-up is not required for patients who go off protocol treatment with iCPD, except to document ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies). For patients who go off protocol treatment with CR/iCR, PR/iPR, SD/iSD or iPD ongoing and have not already started other systemic therapy, follow-up will be required every 3 months until relapse (see Section 5 for investigations to be performed). Please note for patients who go off protocol treatment with iUPD, confirmatory scans should be performed at least 4 weeks, but no longer 8 weeks, after iUPD was documented.

Final report (Form 6) will be required for all patients while study is open. Due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Radiology Review

At the conclusion of the trial, a central review of x-rays and/or scans may be carried out if any responses have been claimed. For purposes of reporting, the results of both local and central radiology reviews will be included.

11.2 Central Pathology Review

There will be central pathology review for this study. Expert pathology review will be done for all patients to confirm the original diagnosis. At least one disease site specialty pathologist with recognized diagnostic expertise for the tumour type will review digital image from the original/recut HE slides and pathology report of the case. Another expert pathologist will be consulted to resolve significant diagnostic discordance if it arises. Results of the central pathology review will not be provided to the originating institution, the patient or patient record. The consistency of diagnosis of rare tumours will be assessed through central review of pathology specimens.

11.2.1 Patients with questionable local pathology (i.e. uncertain as to rare tumour diagnosis) *MUST have their pathology reviewed by a Central Reference Pathologist to confirm eligibility BEFORE the patient can be registered on this study*.

11.2.2 Archival primary tissue block or the following materials, will be required for central pathology review:

- Original slides or one H&E stained re-cut on all tissue blocks (representative formalin-fixed - if formalin is unavailable B5 block may be submitted).
- Five unstained slides (pretreated for immunostaining) from each representative formalin-fixed tissue block. 5 additional unstained slides if B5 block is available and formalin is unavailable.
- Copy of all pathology reports.
- Copy of any ancillary reports, whether performed on the tissue, (i.e. immunophenotyping, cytogenics, molecular genetics, FISH etc.).

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the IND.228 trial specific website, which will include details regarding sample preparation, handling and shipping.

Specimens collected may be used by researchers to better understand the nature of rare cancers and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of registration to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

12.1 Protocol-Mandated Correlative Studies

12.1.1 *Tissue Collection (Mandatory)*

Archival Tumour Collection:
The submission of a representative block of the diagnostic tumour tissue at the request of the CCTG Central Tumour Bank is mandatory for participation in this trial**.** One tumour block and one adjacent normal tissue block are requested from any of the biopsies or resections of the tumour. If no primary cancer blocks are available, one block of metastatic tissue can be sent instead. The preferred tumour sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy.

Blocks are the preferred material to collect, as it is well known that tissue materials (including protein and nucleic acid integrity) on unstained sections deteriorate rapidly within 3-6 months after preparation. This will optimize the amount of tissue available to investigators and permit the preservation of the block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to registering of the first patient to allow cores (two 2 mm cores of tumour from the block) and slides (see Section 11.0 for slide specifications) of representative tumour tissue to be substituted in response to the Central Tumour Bank request.

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

Planned Priority Assays on Tumour Tissue Include:

- PD-1, PD-L1.
- Evaluation of lymphocyte infiltration (TILs) including subtypes by immunohistochemistry (CD8 and FOXP3).
- Expression profiling of immune markers
- Genomic profiling.

12.2 PD-L1 and TILs Pre-Screening - Tumour Tissue
Mandatory for Cohort 2 patients only.

Pre-screening for PD-L1 and TILs can occur at any time prior to registration. All patients must sign the pre-screening consent prior to tissue being sent.
The screening tests will be performed on slides created from an archival tumour block.

The TILs infiltration will be assessed on H&E slides and PD-L1 and expression will be performed by quantitative immunohistochemistsry (IHC). Results will be made available within about 14 days.

Patients will not be identified by name. The only identification on the tissue will be a patient study number assigned at the time of registration to the trial, the surgical/histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. A copy should be submitted with the Baseline Folder

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out.

Please refer to the IND.228 Laboratory Manual for details.

12.3 Blood Collection

The CCTG is interested in exploring the use of surrogate tissues such as serum and plasma in evaluating potential prognostic or predictive biomarkers, or as evidence of pharmacodynamics effects. Serum samples will be collected for planned studies from all patients.

Exploratory assays include:

- Genomic aberrations (mutations, copy number changes) from circulating cell-free DNA (cfDNA).

Detailed instructions for sample acquisition, preparation, and shipping are found in the IND.228 Laboratory Manual.

12.4 Genomic Analyses

Genomic analyses will be performed on tumour and normal DNA. Technologies for genome sequencing are rapidly evolving and the most appropriate methods will be considered at the time of execution. Methods available include: Copy Number Variation, Structural variation, Targeted sequencing of specific gene sets, Hybridization capture and high-throughput PCR, Exome sequencing, Whole genome sequencing.

12.5 Statistical Analysis

The relationships between the tumour response and genetic mutation statuses will be investigated using Fisher's exact test, while the relationships between the time to progression and genetic mutations will be investigated using the log-rank test. Statistical testing will not be conducted in this hypothesis generating evaluation.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

This is a phase II study to investigate the efficacy of durvalumab and tremelimumab in 8 cohorts of patients with rare tumours. The study will accrue up to 160 patients in one treatment arm. Each disease cohort will be evaluated independently.

In order to minimize the expected number of patients treated in the event that the regimen proves to be very disappointing or very unsuccessful, a two-stage design will be used for patient accrual *[Simon 1989]*.

13.2 Primary Endpoints and Analysis

Primary endpoint of this study is objective response rate, defined as the proportion of response evaluable patients who had complete response (CR) or partial response (PR) as their best response as assessed by RECIST version 1.1 criteria (i.e. a 30% decrease in the sum of the longest diameters of the target lesions maintained for at least 4 weeks (CR), or complete disappearance of disease and cancer related symptoms, also maintained for at least 4 weeks (CR)). Early progression is defined as progressive disease at or prior to the first assessment. The exact 95% confidence interval for the response rate will be calculated. The median and range of the duration of response, defined as the time from date of CR or PR to the date when progression or death is observed, will be estimated based on Kaplan-Meier method.

Sample Size for Each of 8 Disease Cohorts

Stage 1 of Accrual: 10 response evaluable patients will be entered in the first stage. Using response hypotheses of $H_0 \leq 5\%$ and $H_a \geq 25\%$, we would reject the drug at the end of the first stage of accrual if no responses were seen. Otherwise, additional 10 patients will be accrued to the cohort.

Stage 2 of Accrual: Additional 10 response evaluable patients will be accrued. We would accept the drug as active if four or more responses are observed from 20 patients accrued.

Significance Level and Power: The procedure described above tests the null hypothesis (H0) that the response rate is 5% versus alternating hypotheses (H1) that the response rate is 25%. The significance level (i.e. the probability of rejecting H0 when it is true) is α=0.02 and the power (i.e. the probability of rejecting H0, i.e. deciding the regimen is active, when H1 is true) is 0.76. In addition, if the true response rate of an agent is 10%, it would be identified as ineffective with probability of 0.87. If the true response rate of the agent is 30%, it would be identified as effective with probability of 0.88.

Since the eligibility will not initially be limited to patients with tumours expression of PD1/PDL1 and or TILs (with the exception of cohort 2); before closing the original cohort when no response was observed after the first stage of the accrual, where feasible, a minimum of 10 patients with tumours with TILs and/or PD-L1 expression will be included in the response analysis. This modified cohort may be expanded to the second stage of accrual if there is at least one response observed.

Accrual and Duration of Study

A minimum of 10 and maximum of 20 response evaluable patients per cohort will be accrued. Should a disease cohort meet or exceed its activity goal, and recruitment is not limiting, additional enrollment beyond 20 patients/cohort may be considered to improve the estimate of anti-tumour activity and exploration of biomarkers outcome correlations. Evidence of anti-tumour response in the first stage will lead to the implementation of *optional* fresh tumour biopsies in patients subsequently enrolled to allow for more detailed genomic analyses. If an unusually high level of activity is seen (i.e. > 4/10 patients with objective response) the data will be made available to AstraZeneca for regulatory submission.

Following a survey of the CCTG IND members, the minimum estimated recruitment is 10 patients/year/cohort. If after 2 years, fewer than 10 patients have been registered in any given disease cohort and no responses have been observed, that cohort will close to accrual due to lack of enrolment. The minimum number of patients recruited is estimated to be 70 and the maximum number is estimated to be 140, assuming some patients will be registered, while some cohorts will close early for inactivity or lack of accrual feasibility. The maximum number will be increased if there are cohorts which will be modified to include patients with TILs and/or PD-L1 expression or additional enrolment beyond 20 patients/cohort is considered.

Patients will be accrued from approximately 15 cancer treatment centres across Canada over a period of approximately 24-48 months.

Following accrual of 20 eligible patients on the OCCC cohort, it was decided to expand the sample size to include 20 additional patients since with a total of 40 evaluable patients, the half-length of the 95% confidence interval for the response rate would be reduced from 21% with 20 patients to 15% when the observed response rate is 35%. Exploratory analysis will assess for correlations between biomarkers and objective response.

13.3 Analysis of Secondary Endpoints: Efficacy Outcomes

Following completion of the study, the following will be described:

- The median and range of the duration of stable disease, defined as the time from date of stable disease as the best response to the date when progression or death is observed, based on Kaplan-Meier method.
- The median and its 95% confidence interval for time to progression, defined as time from the date of randomization to the date of progression, based on Kaplan-Meier method.
- The median and its 95% confidence interval for progression free survival, defined as time from the date of randomization to the date of progression or death, based on Kaplan-Meier method.
- The median and its 95% confidence interval for overall survival, defined as time from the date of randomization to the date of death , based on Kaplan-Meier method.

13.4 Analysis of Secondary Endpoints: Translational Research

Primary tumour tissue specimens and baseline blood samples, will be obtained from all subjects prior to first dose for genetic analysis and other evaluation..

Genetic abnormalities common to the rare tumours and relevant to the mechanisms of action or resistance of the drugs and possibly other putative predictors of response will be assessed. The relationship between these markers and objective response will be explored. Statistical testing will not be conducted in this hypothesis generating evaluation.

Data from the correlative studies will be sent from the central laboratory(ies) to the CCTG for incorporation into the trial database.

Central review of the pathology specimens will be done and we will assess the consistency of diagnosis of rare tumours through central review of pathology specimens.

13.5 Safety Monitoring

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

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 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 AstraZeneca, 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.

14.1.2 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)."

14.2 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).

14.3 Submission of Material for Presentation or Publication

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

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 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).

15.2 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.

15.3 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.

15.3.1 *Obtaining Consent for Pregnancy*

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

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

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

Obtaining Consent for Research on Children

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

15.4 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.

15.5 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.

15.6 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.

15.7 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.

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

The drug company, AstraZeneca, has reserved the right to audit CCTG activities. If AstraZeneca requests to audit participating centres they can only do so after consultation with CCTG and can only perform the audit as a co-audit with CCTG.

15.8 Case Report Forms

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.228 area of the CCTG web-site (www.ctg.queensu.ca).

16.0 REFERENCES

Antonia S, Goldberg SB, Balmanoukian A et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016 Feb 5. pii: S1470-2045(15)00544-6. doi: 10.1016/S1470-2045(15)00544-6. [Epub ahead of print].

Antonia S., Ou S.-H., Khleif S.N., Brahmer J., Blake-Haskins A., Robbins P.B., et al. Clinical activity and safety of MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody, in patients with NSCLC. Poster presented at the European Society for Medical Oncology (ESMO) Annual Meeting, Madrid, Spain, September 26–30, 2014. Ann Oncol. 2014;25(suppl 4):iv466 (1325P).

Brahmer JR, Tykodi SS, Chow LQ et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.

D'Angelo SP, Tap WD, Schwartz GK et al. Sarcoma Immunotherapy: Past Approaches and Future Directions. Sarcoma Volume 2014, Article ID 391967, 13 pages.

Dancey J, Krzyzanowska MK, Provencher DM et al. NCIC CTG IND.206: A phase II umbrella trial of sunitinib (S) or temsirolimus (T) in advanced rare cancers. J Clin Oncol 33, 2015 (suppl; abstr 2594).

Disis ML, Patel MR, Pant S, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with previously treated, recurrent or refractory ovarian cancer: A phase Ib, open-label expansion trial. J Clin Oncol. 2015;33 (suppl; abstr 5509).

Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via CTLA-4 and PD-1 pathways. Immunol Rev 2008;224:166-182.

Fife BT, Pauken KE, Eagar TN et al. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. Nat Immunol 2009;10:1185-1192.

Hampig Raphael Kourie, Gil Awada, Ahmad Hussein Awada. Unknown primary tumors: is there a future therapeutic role for immune checkpoint inhibitors? Future Oncology. February 2016 ,Vol. 12, No. 4, Pages 429-431 ,

Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A. et al. safety and antitumour Activity of Ati-PD-2 Antibody, nivolumab in patients with platinum-resistant ovarian cancer.

Heong V, Njoi N , Tan D. Update in immune checkpoint inhibitors in gynecological cancers. J Gynecol Oncol. 2017. 28(2) e20.

Hodi FS, O'Day SJ, McDermott DF et al., Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.

Ibrahim R, Stewart R and Shalabi A. PD-L1 Blockade for Cancer Treatment: MEDI4736. Semin Oncol 2015;42:474-483.

Johnson DB, Peng C, Abramson RG, Ye F, Zhao S, Wolchok JD, Sosman JA, Carvajal RD, Ariyan CE. Clinical Activity of Ipilimumab in Acral Melanoma: A Retrospective Review. AU. SO Oncologist. 2015 Jun;20(6):648-52. Epub 2015 May 11.

Kansara,M, Teng. W, Smyth. M, Thomas D Translational biology of osteosarcoma. Nature Reviews Cancer. 2014.14; 722–735.

Kirkwood JM, Lorigan P, Hersey P, Hauschild A, Robert C, McDermott D, et al. Phase 2 trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. Clin Cancer Res. 2010;16:1042-8.

Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.

Larkin J, D'Angelo S, Sosman JA, et al. Efficacy and safety of nivolumab (NIVO) monotherapy in the treatment of advanced mucosal melanoma (MEL). Pigment Cell Melanoma Res. 2015; 28(6):789

Lian B, Guo J. Checkpoint inhibitors in treatment of metastatic mucosal melanoma. Chin Clin Oncol 2014;3:37.

Lim J, Poulin NM and Nielsen TO. New Strategies in Sarcoma: Linking Genomic and Immunotherapy Approaches to Molecular Subtype. Clin Cancer Res. 2015;21:4753-9.

Matthew J. Hawryluk, Kai Wang, Depinder Khaira, Juliann Chmielecki, Siraj Mahamed Ali, Julia Andrea Elvin, Jo-Anne Vergilio, Roman Yelensky, Doron Lipson, Vincent A. Miller, Philip J. Stephens, Jeffrey S. Ross; Comprehensive genomic profiling of salivary gland adenocarcinomas to reveal frequency of druggable targets. J Clin Oncol 33, 2015 (suppl; abstr 6040)

Morris VK, Ciombor KK, Salem ME et al. NCI9673: A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA) J Clin Oncol 34, 2016 (suppl; abstr 3503).

Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of ifalimumab, an investigational anti-interferon-α monoclonal antibody, in systemic lupus erythematosus. Clinical Pharmacokinet, 2013 Nov;52(11)1017-27.

Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006 Jun;23(6):1275-84.

Oda K, Hamanishi J, Matsuo K, Hasegawa K.. Genomics to immunotherapy of ovarian clear cell carcinoma: Unique opportunities for management. 2018. *Gynecol Oncol*. 151(2) 381-389.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Rettig EM, Talbot CC Jr, Sausen M, Jones S, Bishop JA, Wood LD, Tokheim C, Niknafs N, Karchin R, Fertig EJ, Wheelan SJ, Marchionni L, Considine M, Fakhry C, Papadopoulos N, Kinzler KW, Vogelstein B, Ha PK, Agrawal N. Whole-Genome Sequencing of Salivary Gland Adenoid Cystic Carcinoma. Cancer Prev Res (Phila). 2016 Apr;9(4):265-74.

Ribas A, Kefford R, Marshall MA, Punt CJA, Haanen JB, Marmol M, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol. 2013;31;616-22.

Robert C, Luc T, Bondarenko I et al. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. N Engl J Med 2011;364:2517-2526.

Seymour L, Bogaerts J, Perrone A et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:143-52

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.

Smith, DA. and Germolec DR. Introduction to immunology and autoimmunity. Environ Health Perspect, 1999. 107 Suppl 5:661-5.

Stewart R, Morrow M, Hammond SA, et al. Identifi cation and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3:1052–62.

Tarhini AA. Tremelimumab: a review of development to date in solid tumours. Immunotherapy 2013;5:215-29.

Topalian SL, Hodi FS, Brahmer JR et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.

Van Morris AM, Luis Vence, Jorge Blando, Robert A. Wolff, Aki Ohinata, Chimela Ohaji, James Allison, Padmanee Sharma, Cathy Eng: NCI#9673 phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal: Immunologic correlates of response 2016 AACR Annual Meeting. New Orleans, abstract CT131

Wang E, Kang D, Bae KS, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamic analysis of tremelimumab in patients with metastatic melanoma. JClin Pharmacol 2014;54(10):1108-16.

Wang D, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009Sep;49(9):1012-24.

Wolchok J, Kluger H, Callahan MK et al. Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med 2013;369:122-133.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumours: Immune-Related Response Criteria. Clin Cancer Res 2009;15:7412-7420.

Zhang S, Shi, R, Li, C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012Jan;52(1):18-28.

APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

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

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

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

APPENDIX II - DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED, INFUSION RELATED AND NON IMMUNE-MEDIATED REACTIONS

(MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy)

The Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion Related and Non Immune-Mediated Reactions can be downloaded at:
DoseMod-ToxicityMgmntGuidelines_28Oct2021.pdf

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution

Durvalumab and tremelimumab will be supplied by AstraZeneca to the distributor, Bay Area Research Logistics (BARL), and distributed by BARL to participating centres.

Drug Labelling

Drug supplies for this study will be labelled in accordance with Health Canada regulations.

Initial Drug Supply

Once a centre is locally activated (following receipt and review of all required documentation), CCTG will authorize a start-up supply of durvalumab and tremelimumab to be shipped directly to the centre. 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 and drug re-order forms will be available on the IND.228 trial website.

Drug Ordering (Re-supply)

Subsequent requests for more drug should be made by authorized personnel at each centre. A copy of the Request for Drug Shipment form (available on the IND.228 trial website) should be faxed to the distributor.

Please allow sufficient time for shipment of drug. Note: shipment will not be made on Fridays and weekends.

Drug Accountability

The investigational products are to be prescribed only by the Qualified Investigator and /or Co-Sub-Investigators having this delegated duty 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, dispensation, return and/or destruction of the investigational product and for the disposition of the product (utilizing the Drug Accountability Log, available on the IND.228 trial website). At the end of the study, it must be possible to reconcile shipment records with records of usage/returned stock by completion of the study drug accountability form. Any discrepancies must be accounted for and documented.

Drug Destruction

Drug Destruction of Patient Returns
Unused trial medication returned by the patient may be destroyed per local policy, AFTER accountability and reconciliation has been completed and documented by the site. Documentation of destruction must be kept on file in the site pharmacy and is subject to on site monitoring/audit.

Drug Destruction of Expired Medication

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

** PLEASE NOTE **
DRUG FROM THIS SUPPLY IS TO BE USED
ONLY FOR PATIENTS REGISTERED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy and appropriate storage is available. 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 10.0 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.228 area of the CCTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial are:

Electronic Case Report Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool*
BASELINE REPORT	Due within 2 weeks of patient registration.	Copies of signature pages of main and pre-screening consent forms; relevant pathology & radiology reports.
TREATMENT REPORT	To be completed every 3 weeks (i.e. after each cycle). Due within 2 weeks of end of course. This report documents treatment, adverse events, investigations and response assessment for each course.	Relevant radiology reports.
CORRELATIVE STUDIES	See Section 12.	
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.	Relevant radiology reports.
FOLLOW-UP REPORT	Continued in-person 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 treatment with response, stable disease ongoing, or unconfirmed progression, Follow-up Report to be completed every 3 months until relapse/progression. 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.
FOLLOW-UP FOR SURVIVAL	Follow-up for survival will continue every 3 months for 2 years (e.g. by telephone).	
DEATH REPORT**	Required for all patients while study is open. Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT (SAE) REPORT	All reportable serious adverse events must be reported as described in Section 9.0. 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.

* Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically.

** NB It is the investigator's responsibility to investigate & report the date/cause of death of any patient who dies during this period. Any death that occurs during this protocol therapy or within 30 days after last dose must also be reported as a Serious Adverse Event as described in Section 10.0.

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 - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

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

APPENDIX VII - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial as well as any associated sub-studies should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

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

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

Minor Protocol Deviations:

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

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

Note:

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

LIST OF CONTACTS

PATIENT REGISTRATION

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

	Contact	Tel. #	Fax #
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Joana Sederias Study Coordinator, CCTG Email: jsederias@ctg.queensu.ca or: Dr. Janet Dancey Senior Investigator, CCTG Email: jdancey@ctg.queensu.ca	613-533-6430	613-533-2411
STUDY CHAIR	Dr. Abha Gupta Abha.gupta@sickkids.ca	416-813-7744	416-813-5327
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Janet Dancey Senior Investigator, CCTG or Joana Sederias Study Coordinator, CCTG	613-533-6430	613-533-2411
DRUG ORDERING See Appendix IV for full details.	See Appendix III and trial website: http://www.ctg.queensu.ca/trials/ind/228/228.html for details and contact information		
ELECTRONIC DATA CAPTURE (EDC) AND RIPPLE (technical support)	CCTG Home Page (Toolbox): https://scooby.ctg.queensu.ca Email Support Staff at: support@ctg.queensu.ca		