ADMINISTRATIVE UPDATE #3: 2020-DEC-04
CCTG TRIAL: IND.232

HEALTH CANADA SUBMISSION: 2016-APR-26
AMENDMENT #1: 2017-JUN-05
ADMINISTRATIVE UPDATE #1: 2018-JAN-10
ADMINISTRATIVE UPDATE #2: 2019-NOV-14

CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II STUDY OF DURVALUMAB (MEDI4736) WITH OR WITHOUT TREMELIMUMAB IN PATIENTS WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER

CCTG Protocol Number: **IND.232**

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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 contains information that is confidential and proprietary to AstraZeneca.

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

I will provide copies of the protocol and access to all information furnished by CCTG and 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.

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

_____ _____

Qualified Investigator
(printed name and signature)

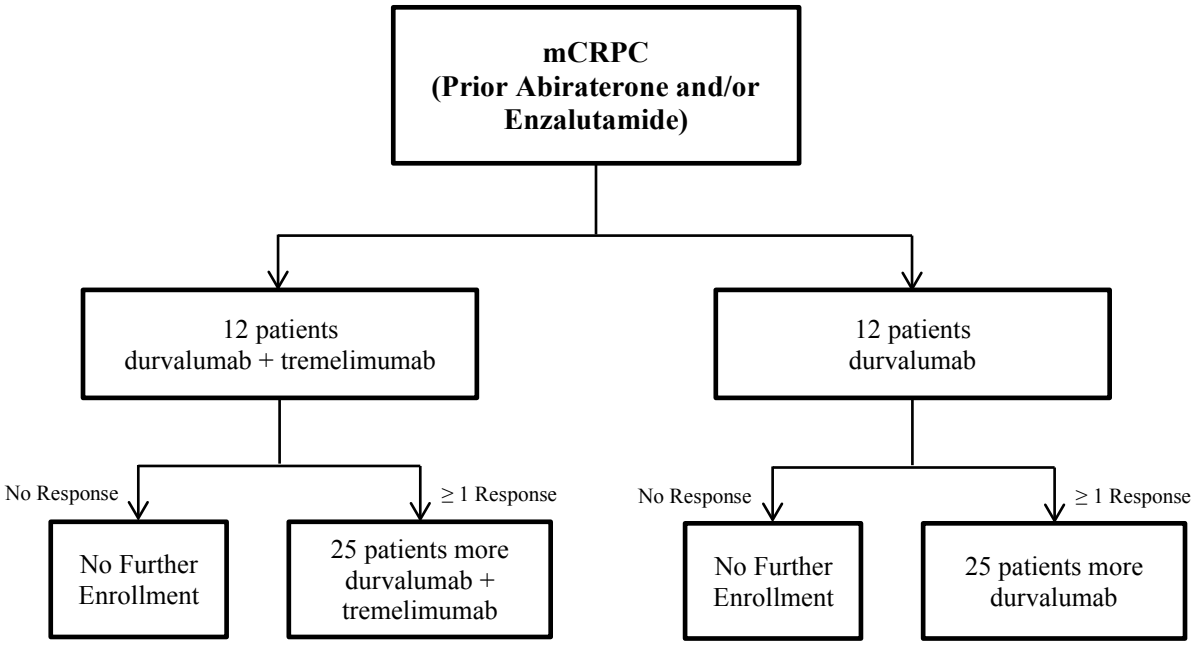
Date

Protocol Number: CCTG IND.232

CENTRE: _____

TREATMENT SCHEMA

This is an open label multi-centre, phase II trial of durvalumab ± tremelimumab in patients with metastatic castration resistant prostate cancer (mCRPC).



1.0 OBJECTIVES

1.1 Primary Objective

To determine the objective response rate (RECIST 1.1 and iRECIST) in patients with metastatic castration resistant prostate cancer (mCRPC) treated with durvalumab alone or in combination with tremelimumab.

1.2 Secondary Objectives

- To determine the prostate-specific antigen (PSA) response rate as time to PSA progression.
- To evaluate time to objective disease progression.
- To evaluate the toxicity and tolerability of durvalumab alone or in combination with tremelimumab.

1.3 Exploratory Objectives

- To explore the utility of tissue and blood based biomarkers to select patients for treatment with durvalumab alone or in combination with tremelimumab.

2.0 BACKGROUND INFORMATION AND RATIONALE

The current standard first-line therapy for patients with metastatic castration resistant prostate cancer (mCRPC) is therapy with androgen receptor antagonist therapies (ARAT) such as abiraterone acetate and enzalutamide (ENZ). Other agents that have shown improvements in overall survival include chemotherapy with docetaxel and cabazitaxel *[Beer 2014, Ryan 2013, Tannock 2004]*. Many patients do not receive chemotherapy because of advanced age and co-morbidities. The radiopharmaceutical radium-223 has recently been approved for use in patients with painful bone metastases without visceral metastases or significant nodal disease. Although a survival benefit was observed, the median time to progression was similar to placebo *[Parker 2013]*.

A dendritic cell based vaccine has been demonstrated to improve overall survival in patients with mCRPC, suggesting that an immune based approach is of relevance in the disease. This vaccine strategy has not seen widespread adoption due to availability and cost issues, but also the lack of any benefit on response, progression or symptom endpoints *[Kantoff 2010]*. This vaccine is not licensed in Canada. Trials with the immune checkpoint inhibitor ipilimumab are in phase III testing in mCRPC currently *[Kwon 2014].* The first trial with ipilimumab in chemotherapy experienced patients was negative, although the subset of patients without liver metastases did have an overall survival advantage *[Small 2007]*.

Initial phase I experience with PD-1/PD-L1 blockade in patients with mCRPC did not demonstrate any significant response rates *[Topalian 2012]*, but this experience is clearly limited. Notably, all these studies were performed prior to the availability of abiraterone and enzalutamide.

CTLA-4 is a co-inhibitory receptor expressed on activated T cells and regulates early stage T cell activation, reducing the amplitude of T cell activation. Ipilimumab, a FDA-approved fully human monoclonal antibody (IgG1) that blocks CTLA-4 to promote antitumour immunity, has received indication in patients with unresectable or metastatic melanoma based on improved overall survival *[Hodi 2010, Robert 2011]*. Clinical trials of ipilimumab in patients with mCRPC have demonstrated some clinical activity, but have largely been disappointing to date. In a phase III trial 799 were randomly assigned to ipilimumab or placebo in post-docetaxel mCRPC; the primary endpoint was overall survival (OS). Patients receiving ipilimumab had a median OS of 11.2 months versus 10.0 months in the placebo group; results were not statistically significant (Hazard Ratio [HR] = 0.85, 95% CI 0.72-1.00; p=0.053).

Tremelimumab is a human IgG2 monoclonal antibody 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. Combinations of durvalumab and tremelimumab appear tolerable at doses of durvalumab 20 mg q4w and tremelimumab 1 mg/kg q4w. Higher doses did not result in greater antitumour activity but were generally associated with higher rates of AEs. Related Grade 3/4 events were reported in 4/18 (22%) patients, while the most frequently reported events were diarrhea, pruritus, rash, and elevated AST/ALTs (11% for each AE). Only one patient discontinued study therapy due to drug-related AEs *[Antonia, 2015]*.

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 2009]*. 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-L1/ PD-1 engagement, has been shown to induce tumour regression across many cancer types, including melanoma and renal cell, colon and lung cancers *[Pardoll 2012, Brahmer 2012]*. Single agent immunotherapy with anti-PD-1 or anti-PDL-1 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 *[Antonia 2014]*. Currently, Nivolumab and Pembrolizumab, an anti PD-1 and anti PD-L1 respectively, have received FDA approval for patients with unresectable or metastatic melanoma, patients with metastatic NSCLC and patients with metastatic renal cell carcinoma *[Wolchok 2013, Postow 2015, Robert 2015, Larkin 2015, Brahmer 2015, Borghaei 2015, Motzer 2015]*.

Durvalumab is a novel IgG1-kappa PD-L1 inhibitor with potent and specific binding to PD-L1 at picomolar concentrations and has directed mutations in the Fc region, limiting off-target cytotoxicity in PD-L1-expressing immune cells *[Khleif 2013; Stewart 2011]*. Surrogate anti-PD-LI antibodies have been shown to increase T-cell activation in vitro by blocking PD-L1/PD-1 engagement and inducing anti-tumour responses in tumour-bearing mice, with corresponding changes in peripheral immune markers. Durvalumab has also been shown to inhibit tumour growth in vivo xenograft models. In a phase I dose escalation study in advanced solid tumours evaluating doses (0.1-15.0 mg/kg every 2 weeks (q2w) or 3 weeks (q3w)), signals of durable clinical activity have been observed in the NSCLC expansion cohort *[Antonia 2016]*.

Combination of anti-PD-L1 and anti-CTLA-4 is a promising approach because of non-redundant pathway blockade and synergy based on preclinical data as well as emergent clinical data, including in unresectable or metastatic melanoma and NSCLC where increase responses were observed with the combination although incremental toxicity is a concern *[Pardoll 2012; Antonia 2015]*. In patients with unresectable or metastatic melanoma the rate of confirmed objective response was 61% in the group that received both ipilimumab and nivolumab versus 11% in the group that received ipilimumab and placebo; progression free survival (PFS) was also significantly longer (HR=0.40; 95% CI 0.23-068; p<0.001). However this benefit was accompanied by a significant increment in toxicity, drug-related adverse events of grade 3 or 4 were reported in 54% of the patients who received the combination therapy as compared with 24% of the patients who received ipilimumab monotherapy *[Postow 2015]*. A phase Ib study of Durvalumab plus tremelimumab in non-small cell lung cancer has been reported; Durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1mg/kg showed a manageable tolerability profile, with antitumour activity irrespective of PD-L1 status, and was selected as the dose for phase III studies *[Postow 2015]*.

Recently, it has been described that PD-L1 becomes highly expressed in enzalutamide resistant prostate cancer and patients progressing on enzalutamide had significantly increased PD-L1/2+ dendritic cells (DC) in blood compared to those naïve or responding to treatment *[Bishop 2015]*. These data support previous pre-clinical results, in which significantly increased circulating PD-L1/2+ DCs and a high frequency of PD-1+T cells in mice bearing enzalutamide-resistant (ENZ-R) tumours were found. ENZA-R tumours expressed significantly increased levels of tumour-intrinsic PD-L1. The expression of PD-L1 on ENZ-R cells, or the ability to modulate PD-L1/2+ DC frequency, was unique to ENZ-R cell lines and xenografts that did not show classical activation of the androgen receptor. These results suggest that ENZ resistance is associated with the strong expression of anti-PD-1 therapy targets in circulating immune cells both in patients and pre-clinical models. We hypothesize that mCRPC progressing after therapy with ENZ or abiraterone may be more sensitive to PD-1/PD-L1 blockade.

With this rationale, we plan a randomized trial in patients with mCRPC progressing after enzalutamide and/or abiraterone acetate to evaluate the antitumour activity of durvalumab alone or in combination with tremelimumab.

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 program cell death 1 (PD-1; CD279) and CD80 (B7-1).

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 C1q 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.

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 5000 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, 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 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.232 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.232 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. This is not expected to be applicable to this trial of males with mCRPC.

4.0 STUDY POPULATION

Patients will have documented evidence of metastatic castration resistant prostate cancer.

4.1 Eligibility Criteria

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

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

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

4.1.1 Patients must have histologically confirmed adenocarcinoma of the prostate that is castrate resistant.

4.1.2 Disease progression as defined as one or both of the following:

PSA Progression:

A rising PSA with 2 subsequent rises over a reference value (not necessarily consecutively), measured a minimum of one week apart. The PSA that confirms progression must have a value of $\geq$ 2 ng/ml (μg/L).

OR

Objective Progression

- RECIST 1.1 or
- PCWG 3 Criteria for bone progression

4.1.3 Patients must be surgically or medically castrated, with testosterone levels of < 50 ng/dL (< 1.7 nM). Patients who have not undergone orchiectomy must continue (or restart if previously discontinued) LHRH therapy throughout the study.

4.1.4 All patients must have a tumour block from their primary or metastatic tumour available and consent to release the block/recently cut slides for correlative analyses (See Section 12.0) and the centre/pathologist must have agreed to the submission of the specimen(s). The site of planned biopsy must not be the measurable lesion (see Section 4.1.5).

4.1.5 Presence of clinically and/or radiologically documented disease. All radiology studies must be performed within 28 days prior to randomization (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)	$\geq$ 10 mm	→ longest diameter
Lymph nodes by CT scan	$\geq$ 15 mm	→ measured in short axis

4.1.6 Patients must be ≥ 18 years of age.

4.1.7 ECOG performance status 0 or 1.

4.1.8 *Prior Therapy*

Systemic Therapy:
0-1 prior regimen of cytotoxic chemotherapy in the CRPC setting is permitted..

Hormonal Therapy:

- Patients must be castrate resistant.
- Have failed/progressed on prior abiraterone and/or enzalutamide.
- Patients must have discontinued anti-androgens for at least 4 weeks prior to study entry (at least 6 weeks for bicalutamide).

Other therapy:
Prior treatment with other agents, such as tyrosine kinase or other targeted agents is permissible.

- Systemic corticosteroids are permitted at a dose equivalent to ≤ 10 mg prednisone daily and are only permitted for reasons other than prostate cancer treatment (ex: fatigue, anorexia, etc.); topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are permitted.
- Bisphosphonates / denosumab are permitted for treatment of hypercalcemia, osteoporosis and skeletal-related events

Immunotherapy:
Patients may not have received prior immune check point inhibitors (anti PDL1 and anti CTL-4). Vaccines and treatment with oncolytic viruses is permissible.

Patients must have recovered from all reversible toxicity related to prior systemic therapy (chemotherapy and hormone) and have adequate washout as follows:

Longest of one of the following:

- Two weeks;
- The longer of 30 days or 5 half-lives for investigational agents;
- Standard cycle length of standard therapies.

Radiation:
Prior external beam radiation or radium-223 is permitted provided a minimum of 28 days (4 weeks) have elapsed between the last dose of radiation and the date of randomization. Exceptions may be made for low-dose non-myelosuppressive radiotherapy after consultation with CCTG. Concurrent radiotherapy is not permitted. Prior strontium-89 at any time is not permitted.

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

4.1.9 *Laboratory Requirements*
(Must be done within 7 days prior to randomization)

Hematology	Absolute neutrophils	$\geq$ 1.5 x 10^9/L
	Platelets	$\geq$ 100 x 10^9/L
	Hemoglobin	$\geq$ 90 g/L*
Chemistry	Bilirubin	$\leq$ 1.5 x ULN (upper limit of normal)**
	AST and ALT	$\leq$ 2.5 x ULN $\leq$ 5.0 x ULN (if patient has liver metastases)
	Serum creatinine *or:* Creatinine clearance***	< 1.25 x ULN $\geq$ 40 mL/min

* Contact CCTG if exception on medical grounds is appropriate to minimize risk of unnecessary transfusion.

** If confirmed Gilbert's, eligible provided ≤ 3 x ULN.

*** Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft and Gault equation below:

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

4.1.10 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. See Section 9.3.1 for additional details.

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.

4.1.11 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 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

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

4.1.13 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. The patient's city of residence may be required to verify their geographical proximity. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

Patients must agree to return to their primary care facility for any adverse events which may occur through the course of the trial.

4.1.14 In accordance with CCTG policy, protocol treatment is to begin within 5 working days of patient randomization.

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 requiring concurrent anticancer therapy.

4.2.2 Patients with brain metastases are not eligible.

4.2.3 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.

4.2.4 History of primary immunodeficiency, history of allogenic organ transplant that requires therapeutic immunosuppression and the use of immunosuppressive agents within 28 days of randomization* or a prior history of severe (grade 3 or 4) immune mediated toxicity from other immune therapy or grade ≥ 3 infusion reaction.

4.2.5 Live attenuated vaccination administered within 30 days prior to randomization or within 30 days of receiving durvalumab.

4.2.6 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.

4.2.7 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%.

4.2.8 Concurrent treatment with other investigational drugs or anti-cancer therapy (except LHRH in patients not surgically castrated).

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.
- Pneumonitis.

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 randomization)	Day 1 each cycle, and as clinically indicated	Every 12 weeks after randomization	4 weeks after completion of protocol therapy	3 month follow-up (only required for pts without confirmed PD and ongoing toxicities[1])	6 month follow-up (required for all patients with confirmed PD)
History and Physical Exam						
Including: height, weight, BSA, performance status, clinical tumour measurements (if applicable)	X	X		X		
Blood pressure, heart rate, temperature	X	X[2]		X		
Laboratory Procedures/Assessments[3]						
CBC, differential, platelets	X	X		X[4]	X[4]	
PTT, PT/INR (if on anticoagulants)	X	X		X[4]	X[4]	
Serum creatinine, bilirubin, AST, ALT, ALP, LDH, albumin, glucose, amylase[5], lipase[5], electrolytes (potassium, calcium, magnesium)	X	X		X[4]	X[4]	
PSA	X[6]	X[7]		X[8]	X[8]	
TSH[9]	X	X				
Testosterone (to confirm biochemical castration only)	X					
Radiology[10,11]						
Chest/abdomen/pelvis CT scan Other scans as necessary to document disease[12]	X (within 28 days prior to randomization or 35 if negative)		X	X	X	
Bone Scan[12,13]	X (within 28 days prior to randomization or 35 if negative)		X	X	X (if positive at baseline and does not yet have confirmed PD)	
Other Investigations						
Urinalysis[14]	X					
LVEF[15]	X (within 28 days prior to randomization)					
Adverse Events	X	Continuously		X	X[1]	
Survival/Anti-cancer Treatment Follow-up						X
Correlative Studies (mandatory)						
Fresh tumour biopsy[16]	X					
Archival Tumour Tissues	X					
Blood Collection	X[17]			X[18]		

footnotes on next page …

1. Every three months thereafter to follow adverse events felt related until resolved to ≤ grade 2.
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. Then 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 parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable as long as the same one is followed throughout.
6. At least three previous PSA values with the interval between of ≥ 4 weeks, should be recorded for the patient to estimate doubling time as well as one prior to registration.
7. PSA should also be done at the end of the last cycle.
8. All patients at 4 weeks. For patients without PSA progression, repeat every 4 to 8 weeks until progression or until new systemic therapy is initiated.
9. Free T3 and free T4 will be measured if TSH is abnormal.
10. 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. 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).
12. Maintain schedule every 12 weeks even if cycles are delayed.
13. Bone scan is required and must be repeated every 12 weeks and end of study, regardless if positive or negative at baseline, as well as when clinically indicated. If NEW bone lesion(s) are noted on the patient's bone scan, see Section 8.5.4 for details.
14. Only as clinically indicated after baseline
15. Only if significant cardiac history (see section 4.2.7)
16. Fresh Biopsy is mandatory for all patients after consent but prior to randomization, see Section 12.0.
17. To be collected after randomization and prior to cycle 1 treatment.
18. To be collected at end of treatment/disease progression

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/RANDOMIZATION PROCEDURES

6.1 Entry Procedures

All randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the IND.232 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.232 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.232)
- 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
- height and weight

6.2 Randomization

Randomization will be provided electronically. This is a parallel cohort phase II study. Patients will be randomized between two cohorts when both cohorts are enrolling. After the interim analysis, depending on the results, patients may be randomized to one of two cohorts, or a single cohort if one has closed.

At the time of randomization, all data reported within the Patient Enrollment folder must be accurate, complete and verifiable against source documentation. If a system query is issued indicating that the patient is not eligible, enrollment within the EDC system will not proceed. CCTG should be contacted for assistance if needed. Under no circumstances should inaccurate data be entered in order to permit randomization.

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 randomization.

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

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 5 working days of patient randomization.

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.

Arm	Agent(s)	Dose	Route	Duration	Schedule
1 & 2	Durvalumab	1500 mg	IV	60 min	Day 1 every 4 weeks
1	Tremelimumab	75 mg	IV	60 min	Day 1, cycles 1-4
Patients with a body weight of less than or equal to 30 kg 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 Adjustments*

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 ± 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, 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 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 that outline dose adjustments for these toxic effects can be found in Appendix II. 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 4.1.9 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*
See Appendix II for full details of toxicity management.

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

1. Treat each of the toxicities with maximum supportive care (including slowing / interrupting / omitting the agent suspected of causing the toxicity where required).
2. If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab ± tremelimumab along with appropriate continuing supportive care.
3. All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition to the detailed toxicity management guidelines described in Appendix II, the following principles are suggested:

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

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

7.1.6 *Management of Infusion Reactions*

Guidelines for management of infusion-related reactions 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 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).

7.3.1 *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 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.
- Bisphosphonates / denosumab are permitted for the treatment of hypercalcemia, osteoporosis and prevention of skeletal related events for patients with bone metastases. However, the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of patient unless disease progression can be completely ruled out.

7.3.2 *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. Patients who exhibit objective disease progression prior to the end of cycle 1 are considered to be 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 *[Eisenhauer 2009]* 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.

See Section 10 for criteria for continuing treatment past RECIST 1.1 disease progression.

8.2 RECIST 1.1 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 Immune-Related modified RECIST criteria. 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* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.2 *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:

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

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 required in this small randomized control trial.

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 2 below).

Table 1: Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes < 10 mm
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 < 10 mm
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.

8.3 iRECIST 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, resulting in previously 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.

8.3.1 *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 progression, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued progression where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions (from uPD):
  - 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);
- RECIST 1.1 criteria are met 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 is 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 3, 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.

8.3.2 *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 meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions 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. These data will enable the development and testing of alternate response criteria, or further modifications of RECIST.

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

Table 2: Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**
CR / iCR	CR	No	CR	iCR
CR/iCR	Non-CR/Non-PD Non-iCR/Non-iUPD	No	PR	iPR
PR/iPR	Non-CR/Non-PD Non-iCR/Non-iUPD	No	PR	iPR
SD/iSD	Non-CR/Non-PD Non-iCR/Non-iUPD	No	SD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	The appearance NLs confirms PD if Additional NLs or iUPD in last TP based on NLs and increase in size (≥ 5 mm for NLT or any increase for NLNT) If no change in NLs from last TP, remains iUPD
PD	Non-CR/Non-PD Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in sum of at least 5 mm, otherwise remains iUPD
PD	PD	No	iUPD	iCPD if further increase in previously identified*** T lesion iUPD ≥ 5 mm and / or NT lesion iUPD
PD	PD	Yes	iUPD	iCPD if further increase in previously identified T lesion iUPD ≥ 5 mm and / or NT lesion iUPD and / or size or number of new lesion
Non-iUPD	Non-iUPD	Yes	iUPD	iCPD if increase in size of previously identified new lesions of increased number of new lesion

* Using RECIST 1.1 principles. If no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.
** In any category.
*** Previously identified in assessment immediately prior to this time-point (TP)
NA = not applicable.

Table 3: iRECIST Best Overall Response (iBOR)

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

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
CR	CR, PR, iUPD, NE	CR/iCR, PR/iPR, iUPD, iCPD, NE	iUPD	iCPD	iCR
iUPD	PR, SD, NE	CR	CR, PR, SD, iUPD, NE	CR, PR, SD, iUPD, iCPD, NE	iCR
iUPD	PR	PR, SD, iUPD, NE	PR, SD, iUPD, NE, cPD	PR, SD, iUPD, NE, iCPD	iPR
iUPD	SD, NE	PR	PR, SD, iUPD, NE	PR, SD, iUPD, iCPD, NE	iPR
iUPD	SD	SD, iUPD, NE	SD, iUPD, iCPD, NE	SD, iUPD, iCPD, NE	iSD
iUPD	iUPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

1. Table assumes a randomized study where confirmation of CR or PR is not required.
2. NE = not evaluable that cycle.
3. Designation "I" for BOR can be used to indicate prior uPD to aid in data interpretation.
4. 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 and Stable Disease 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).

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

8.5 Prostate Response according to PCWG3

(as defined by Scher 2016)

All patients will be evaluable for PSA response provided follow-up PSA values are obtained to allow application of the definitions below *[Bubley 1999]*.

Response: 50% fall in PSA from baseline maintained for ≥ 4 weeks, and without evidence of disease progression documented at time of confirmatory values.

Non Response: Failure to achieve PSA response criteria.

PSA response duration will commence on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 50% above the nadir value, provided that the increase is at least 2 ng/mL (μg/L) (or back to baseline).

8.5.1 *PSA Progression*
(as defined by Scher 2016)

In PSA non-responders: PSA progression is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL (μg/L) or more from the nadir (or baseline if no decrease from baseline is documented), which is confirmed by a second value obtained 3 or more weeks later.

In PSA responders: rise in PSA of 25% (minimum 2 ng/ml (μg/L)) above nadir value and confirmed by a second increasing value obtained 3 or more weeks later.

Time to PSA progression will be calculated from date of randomization to date of PSA progression. If interval PSA values are collected or reported during cycle, only the end of cycle PSA (PSA collected for Day 1) will be used in response evaluation.

NOTE: Because with systemic treatment an initial rise in PSA is followed by a drop, it is recommended patients receive at least 12 weeks of therapy even if PSA is rising, provided no other evidence of progression is seen, palliative radiation is not required and protocol therapy is tolerable (see Section 10.0).

8.5.2 *Clinical Benefit*

Clinical benefit is defined for the purpose of this protocol as one of the following:

- PSA decline ≥ 50%
- Complete or partial objective response
- Stable disease for ≥ 12 weeks

8.5.3 *Clinical Progression*

Clinical progression is defined as the need for palliative radiotherapy, change in anti-cancer therapy, or cancer related decrease in ECOG performance status to ≥ 3.

8.5.4 *Bone Disease Progression*

For the purpose of evaluation of bone disease in this study, a bone scan will be done at baseline and must be repeated every 12 weeks after randomization and at end of study, regardless if positive or negative at baseline.

For progressive disease in bone lesions, if at least 2 new bone lesions are seen by bone scan on the first post treatment scan, then these lesions are confirmed by a second bone scan done 6 or more weeks later that also shows at least 2 additional new bone lesions (2 + 2 rule) then the date of progression is the date of the first post-treatment scan.

For scans after the first post treatment scan, if 2 new bone lesions are visualized, then these lesions need to be seen on a subsequent scan confirming disease progression. If confirmed, the date of PD is the date of the first scan. In general, unequivocal progression of bone lesions will not be accepted as evidence of disease progression unless the criteria above are met and are confirmed.

Additionally, if a new bone lesion(s) are seen on the patient's CT it will also need to be confirmed with a bone scan and will ONLY be considered PD if the criteria above are met.

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, which may be treatment arm dependent. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

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

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

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

8.6.4 *Bone Scan*. ^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy is the standard for bone imaging.

8.6.5 *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.

8.6.6 *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.

8.6.7 *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.

8.6.8 *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 unexpected and 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
- Any immune related adverse event (irAE) requiring high dose steroids is by definition medically significant and must be reported as such.
- 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.232 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.232 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.232 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

9.3.1 *Pregnancy Prevention*

Males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.10. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. 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 is responsible for beginning contraceptive measures.

Females of childbearing potential are defined as those who are not surgically sterile (i.e. bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as 12 months with no menses without an alternative medical cause).

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*

The investigator is required to report to CCTG any pregnancy occurring in female partners of male participants. Pregnancies occurring up to 6 months after the last dose of study treatment must also be reported.

Pregnancy itself - occurring in 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 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, a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

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

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

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.232 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.232 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.232 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 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.
- Patients who are not clinically stable or who have confirmed disease progression (iCPD) 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.

10.2 Duration of Protocol Treatment

- Treatment with durvalumab will continue until disease progression or unacceptable toxicity.
- Patients randomized to durvalumab + tremelimumab will receive durvalumab as above and tremelimumab for cycles 1-4.

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. For patients who go off protocol treatment with iCPD, and have ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies) follow-up will be required every 3 months.

For patients with no ongoing or late toxicities and have confirmed disease progression, follow-up will be required every 6 months for survival data and other anti-cancer treatment only. For patients who go off protocol treatment with CR/iCR, PR/iPR, SD/iSD or iUPD ongoing, and have not already started other systemic therapy follow-up will be required every 3 months until relapse (see Section 5.0 for investigations to be performed) and then every 6 months until death.

Death Report will be required for all patients, due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Data Review

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

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

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

11.2 Central Radiology Review

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

11.3 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the IND.232 trial specific website, which will include details regarding sample preparation, handling and shipping.

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

12.1 Correlative Sample Collection

Summary

Sample	Baseline	Progression/End of Treatment
Archival Tissue*	X	
Fresh Tumour Biopsy*	X	
Whole Blood (cfDNA)**	X	X

* Mandatory for all patients after consent and prior to randomization. If archival tissue cannot be obtained, please contact CCTG.
** Mandatory for all patients after randomization and prior to cycle 1 treatment.

12.2 Protocol-Mandated Correlative Studies

Tissue Collection *(mandatory for all patients)*

Archival Tumour Block/Slides:

The collection of a representative block/slides of the diagnostic tumour tissue (from primary or metastatic tumour) is an important part of this trial. Blocks/slides will be carefully stored at the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario, until the study specific assays are done. All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

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.

Samples will be used for the purposes of this study 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.

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

Centres should contact CCTG if they are unable to submit a tumour block, as sufficient tissue is required for the tests described below. Upon receipt, the CCTG pathology coordinator will then send appropriate material, along with information regarding CCTG protocol number and an assigned unique tumour bank ID number to the research laboratory(ies) where these assays will be done.

Fresh Tumour Biopsies:

ALL patients registered/randomized on the trial will have fresh tumour biopsies performed prior to Cycle 1 treatment. If a bone lesion is the only site of disease possible for biopsy, please contact CCTG to discuss.

Planned priority assays on tumour tissues from all patients include:

- Expression of PD-L1 and T-cell subsets (infiltrating).

Blood Collection:

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

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.232 lab manual.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

The primary objective of this randomized, open-label, and non-comparative phase II trial is to determine the objective response rate in patients with metastatic castration resistant prostate cancer treated with durvalumab alone or in combination with tremelimumab. Secondary objectives include determining the PSA response rate, evaluating the time to progression based on measurable disease, bone progression or PSA, and the toxicity and tolerability in patients receiving durvalumab ± tremelimumab. Patients will be randomized in 1:1 ratio to receive durvalumab alone or in combination with tremelimumab. Between 24 and 74 patients will be enrolled.

13.2 Primary Endpoints and Analysis

The primary endpoint of this study is the objective response rate, using iRECIST criteria defined in Section 8. Objective response rate using RECIST 1.1 will also be reported. 95% confidence interval for objective response rate in both definitions will be calculated.

13.3 Sample Size and Duration of Study

A Simon's optimal two-stage design will be employed for both treatment arms. An objective response rate in either arm of 5% or less would not be of interest for further study (null hypothesis). If the objective response rate for either cohort were 20% or greater, then this would be considered of interest to further evaluate in larger trials (alternative hypothesis). Using an alpha error of 0.1 and a beta error of 0.1, 12 patients per arm will be initially accrued to stage 1. If 1 or more patients had objective response rate on either arm at end of stage 1, the arm will be expanded to a total of 37 evaluable patients. If ≥ 4 measurable responses are observed from these 37 patients in an arm then that arm would be considered for further testing in phase III trials.

If no objective response rates are observed in the first stage of an arm, then PD-L1 expression will be evaluated as a predictive biomarker, and expansion of that arm to 12 patients with PD-L1+ tumours will be considered. If fewer than 4 responses are seen after accrual to the second-stage of the study, then PD-L1 expression in biopsies will be evaluated and expansion of that arm to 37 patients with PD-L1+ tumours will be considered.

13.4 Safety Monitoring

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

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 enrollment 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 Reporting*

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

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

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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_17Nov2020.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 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. The drug will be shipped to the centre within 5 working days of local activation. Note: shipment will not be made on Fridays and weekends.

Resupply

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.232 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 (Drug Accountability Log, available on the IND.232 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 randomization and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see Section 9.0 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.232 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 optional consent forms; relevant pathology & radiology reports.
TREATMENT REPORT	To be completed every 4 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 12.0.	
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 the end of the last cycle date. Due within 2 weeks after contact with patient.	Relevant radiology reports.
3 MONTH 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 or unconfirmed progression ongoing, Follow-up Report to be completed every 3 months until relapse/progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
6 MONTH FOLLOW-UP REPORT	Required for all patients with confirmed PD to confirm survival status and other anticancer treatment.	
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
DEATH REPORT**	Required for all patients 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 and other documentation, as requested..

* Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. 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 9.0.

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 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 #
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*	613-533-6430	613-533-2411
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	James Hutchenreuther Study Coordinator, CCTG Email: jhutchenreuther@ctg.queensu.ca or Linda Hagerman Study Coordinator, CCTG Email: lhagerman@ctg.queensu.ca or: Dr. Lesley Seymour Senior Investigator, CCTG Email: lseymour@ctg.queensu.ca		
STUDY CHAIR	Dr. Sebastien Hotte Study Chair Email: hotte@HHSC.ca	905-387-9495	905-575-6324
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Lesley Seymour Senior Investigator, CCTG or James Hutchenreuther Study Coordinator, CCTG or Linda Hagerman Study Coordinator, CCTG	613-533-6430	613-533-2411
DRUG ORDERING See Appendix III for full details.	See Appendix III and IND.232 website for details and contact information		
ELECTRONIC DATA CAPTURE (EDC) AND RIPPLE (technical support)	CCTG Home Page (Toolbox): https://scooby.ctg.queensu.ca Email Support Staff at: support@ctg.queensu.ca		