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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II STUDY OF CFI-400945 AND DURVALUMAB IN PATIENTS WITH ADVANCED/METASTATIC TRIPLE NEGATIVE BREAST CANCER (TNBC)

CCTG Protocol Number: **IND.239**

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REGULATORY SPONSOR:	CCTG
SUPPORTED BY:	AstraZeneca, University Health Network (drug only)

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

CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).

TABLE OF CONTENTS

STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

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

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

I will provide copies of the protocol and access to all information furnished by CCTG 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 UHN, AstraZeneca and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to UHN, 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, UHN or AstraZeneca with or without cause.

_____ _____

Qualified Investigator
(printed name and signature)

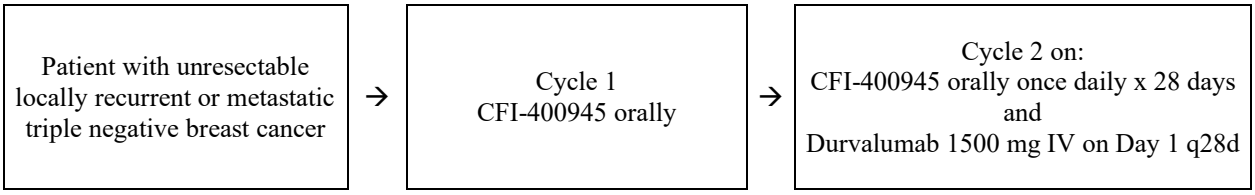
Date

Protocol Number: CCTG IND.239

CENTRE: _____

TREATMENT SCHEMA

This is a multicentre, open-label phase II study of CFI-400945 and durvalumab in patients with advanced or metastatic triple negative breast cancer. Up to 28 patients will be enrolled. This study is being conducted by the Canadian Cancer Trials Group (CCTG) and supported by AstraZeneca and University Health Network (provision of CFI-400945 only).



1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the objective response rate (RECIST 1.1) of CFI-400945 given with durvalumab.

1.2 Secondary Objectives

- To evaluate Disease Control Rate (DCR, defined as CR or PR or stable disease (SD) > 16 weeks in duration) of CFI-400945 given with durvalumab.
- To evaluate the immune-related response rate (iRECIST) of CFI-400945 given with durvalumab.
- To establish the safety and tolerability of CFI-400945 given orally in combination with durvalumab in a q4w schedule and to confirm the recommended phase II dose (RP2D) in patients with metastatic triple negative breast cancer (TNBC).

1.3 Tertiary Objective

- To assess the pharmacodynamic and immune effects of CFI-400945+durvalumab.

2.0 BACKGROUND INFORMATION AND RATIONALE

Recent advancements in the treatment of breast cancer have led to higher rates of cure for early stage disease, and longer survival for those living with metastatic disease. However, there remains a critical need for new and effective therapies for those whose disease is resistant or becomes resistant to currently available options. This need is especially urgent for triple negative breast cancer (TNBC), an aggressive subtype associated with early lethality, for which chemotherapy is the only approved treatment (apart from PARP inhibitors in patients with germline BRCA1/2 mutations).

Studies of anti-PD-1/PD-L1 immune checkpoint inhibitors have shown some monotherapy activity in TNBC, but this is very limited in patients with features of aggressive disease (liver metastases, elevated LDH), and response rates observed in the second line or later setting are ~ 5%. *[Adams 2017(a); Adams 2017(b); Emens 2018]*.

More recently, multiple clinical trials in the neoadjuvant and metastatic settings have evaluated anti-PD-1/PD-L1 antibodies in combination with cytotoxic chemotherapy in TNBC. The first of these to be reported has shown an improvement in progression free survival with the addition of the anti- PD-L1 antibody atezolizumab to nab-paclitaxel chemotherapy. However, since the majority of patients developing metastatic TNBC have received anthracyclines and taxanes in the neo/adjuvant setting, chemoresistance is a major challenge. Thus, non-chemotherapy options could have significant advantages, both in terms of efficacy and treatment-associated toxicity. This study seeks to augment the efficacy of PD-L1 blockade in TNBC by developing a combination of durvalumab with a first in class inhibitor of Polo-like Kinase 4 (PLK4), a cytotoxic small molecule oral therapy with potent pre-clinical activity in TNBC models which can be safely administered to patients with advanced solid tumours *[Mason 2014]*.

PLK4 is an atypical member of the Polo-like serine/threonine kinases and differs from other PLK enzymes in structure and function. PLK4 controls centriole duplication and mitotic progression, and was identified as a drug target based on functional screening to identify vulnerabilities of genomically unstable breast cancers *[Mason 2014; Dominguez-Brauer 2015]*. CFI-400945 was generated as a potent, selective and orally bioavailable inhibitor of PLK4 (PLK4 Ki=0.26 nM) *[Mason 2014; Yu 2015]*, and was advanced into clinical development based on desirable pharmacologic properties and pre-clinical antitumour activity. In vitro, CFI-400945 exhibits potent anti-proliferative effects in cancer cell lines via induction of apoptosis and cell cycle arrest with induction of aneuploidy. In vivo testing of diverse models, including cell line and patient-derived xenografts of breast and ovarian cancer confirmed potent anti-tumour effects at tolerable doses *[Mason 2014]*.

A first-in-human phase I dose escalation study of CFI-400945 evaluated dose levels from 3 to 96 mg/day [NCT01954316]. CFI-400945 was generally well-tolerated, with dose limiting toxicities of neutropenia and asymptomatic lipase elevation (n=1) observed at doses $\geq$ 72 mg/day. No significant treatment-emergent/dose-dependent toxicities other than neutropenia were observed. Evidence of anti-tumour activity was observed in a patient with KRAS mutant colorectal cancer who remained on study for 12 cycles at 48 mg/day (best response -24%), and a patient with AKT1-mutated endometrioid endometrial cancer (best response to any prior therapy had been progressive disease) had a minor response (19% shrinkage of target lesion) for 6 cycles. Long term tolerability has been confirmed, including a patient who remained on trial for over 24 months (48 mg/day). Please refer to the most recent version of the Investigator Brochure for more details.

Unexpected responses to immune checkpoint blockade were observed in 2 patients (KRAS-mut CRC and AKT1-mut MSS endometrial cancer) who had experienced prior tumor shrinkage with CFI-400945. Based on hypotheses that the induction of aneuploidy caused by treatment with CFI-400945 could create an immunogenic stimulus *[Davoli 2017]*, and supported by these clinical anecdotes, where patients pre-treated with CFI-400945 experienced unexpected responses to ICB, the combination of CFI- 400945 and PD-1 inhibition was evaluated in transplantable murine cancer models (MC38 and CT26). In both models, the combination of CFI-400945 and PD-1 blockade resulted in increased antitumour activity compared to either agent alone, as evidenced by an increased rate of tumour regressions. Importantly, specific antitumour immunity was also observed, as demonstrated by resistance to reinoculation of the same cell line.

Durvalumab is a FDA-approved immunotherapy that blocks PD-L1/PD-1 interaction. Its antitumour activity has been observed in many solid tumours *[Massard 2016]*. Development in breast cancer has focused on combinations, including with chemotherapy, targeted therapy (olaparib), and with other immune checkpoint inhibitors (tremelimumab). While no large study of durvalumab in breast cancer has been reported, the largest studies of PD-1 and PD-L1 inhibitors in chemotherapy-pretreated patients with metastatic TNBC have shown response rates in the ~5% range *[Adams 2017(b); Emens 2018]*. The safety and tolerability of durvalumab is well-established, making it an excellent potential combination partner for CFI-400945 for which overlapping toxicities are not expected.

Given the robust preclinical activity of CFI-400945 in TNBC *[Mason 2014]*, the clinical activity of CFI-400945 in advanced solid tumours (with a tolerable and convenient oral dosing schedule), and non-overlapping toxicity with durvalumab, we propose the clinical evaluation of the combination of CFI-400945 plus durvalumab in patients with chemotherapy-resistant TNBC whose tumours are unlikely to benefit from single agent immune checkpoint inhibitor.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 CFI-400945

Consult the most recent version of the investigator brochure for current information.

3.1.1 *Mechanism of Action*

In pre-clinical studies, CFI-400945 was shown to be a selective and potent inhibitor of Polo-like Kinase 4 (PLK4), which regulates centriole duplication. CFI-400945 does not inhibit PLK 1-3 at relevant doses. PLK4 is overexpressed in a variety of solid tumours, and elevated expression is associated with poor clinical outcomes *[Hu 2006; Miller 2005; Van de Vijver 2002]*. Depletion of PLK4 expression in cancer cells by RNA interference leads to mitotic defects and cell death *[Mason 2014]*. Thus, pharmacologic inhibition of this target is expected to produce antiproliferative and cytotoxic effects against cancer cells, as has been observed in mechanistic studies with CFI-400945.

3.1.2 *Experimental Antitumour Activity*

CFI-400945 induces apoptosis and inhibits proliferation of human breast cancer cell lines at nanomolar concentrations. In vivo anti-tumour activity of CFI-400945 has been shown in mice bearing human cancer xenografts of multiple histologies, including robust tumour growth inhibition and durable tumour regression in primary tumour xenografts of breast and ovarian cancer *[Mason 2014]*.

3.1.3 *Clinical Trials*

Human experience with CFI-400945 consists of a dose-finding phase I study (CFI-400945-CL-001) in which subjects with treatment refractory advanced solid tumours were evaluated. As of December 20, 2017, interim safety data are available for a total of 50 subjects treated in 10 cohorts dosed over the range of 3 – 96 mg/day in 28-day continuous cycles. A RP2D of 64 mg/day for the continuous dosing schedule has been established. DLTs in the 72 mg and 96 mg cohorts included G3 neutropenia in both cohorts, G4 febrile neutropenia in the 64 mg and 96 mg cohorts, and asymptomatic G4 lipase elevation in the 72 mg cohort. The common related AEs (≥ 10%) were fatigue, nausea, decreased appetite, diarrhea, neutrophil count decreased and neutropenia. Two possibly related AEs led to study discontinuation; serum amylase/lipase increase (72 mg/day) and febrile neutropenia (64 mg/day). Dose-limiting toxicity (DLT) occurred in four subjects; these were serum amylase/lipase increase and neutropenia (72 mg/day), and two cases of febrile neutropenia (64 mg/day and 96 mg/day). To add an additional safety margin to mitigate risk of early onset myelosuppression seen in a minority of patients, more intensive hematologic monitoring was added to this period, and a 14 day run in (Cycle 0), consisting of 7 days of CFI-400945 dosing followed by 7 days without CFI-400945 dosing was implemented. No cardiac toxicity was observed in the phase I dose escalation or expansion. Please refer to the most recent version of the Investigator Brochure for full details.

3.1.4 *Justification of Dose Selection*

In the first in human phase I study of CFI-400945, 64 mg/day was the determined to be the RP2D, and was the dose selected for the solid tumour expansion cohort. Because of the occurrence of Grade 4 febrile neutropenia in 1 patient in the expansion cohort (1/7 patients treated at 64 mg/day; occurring in a patient with other disease-related factors that may have increased susceptibility to this event), a 14 day run in consisting of 7 days of daily dosing at 64 mg/day followed by a 7-day rest period with no dosing, was implemented to mitigate the small risk of early onset neutropenia. Antitumour activity was observed in the phase I study at doses as low as 48 mg/day.

On this study, a starting dose of 64mg/ day was used. Of the first 5 patients enrolled, 4 had neutropenia. Of these patients, 2 had grade 4 neutropenia within the first cycle, 1 had grade 4 neutropenia within the second cycle and 1 had grade 3 neutropenia within the second cycle. One patient required hospitalization for febrile neutropenia (and growth factors), while a second patient required prophylactic growth factors. Three patients required dose modifications. The study was placed on temporary hold and a safety review was conducted. Other than the usage of a different lot of CFI-400945, the only apparent correlation with clinical factors was a single patient with disease related hepatic dysfunction at baseline. Based upon those data the trial was reopened at 48 mg/day, with a revised dose modification schema, and provision for escalation in selected patients. Six patients were enrolled at this dose level with 5 requiring a dose modification. As a result, the trial was reopened at 40mg/day. Eight patients were enrolled at this dose level. Of these patients, two had grade 4 neutropenia and one had febrile neutropenia. Five patients required a dose hold related to neutropenia and three required a dose reduction related to the neutropenia. As a result, 32 mg/day has been declared as the recommended phase II dose and a safety cohort of six patients will be enrolled prior to opening accrual to additional centres.

3.1.5 *Pharmaceutical Data*

Supplied:
Refer to the Pharmacy Manual for most current information.

Stability and Storage:
CFI-400945 tablets will be packaged into high-density polyethylene or polypropylene bottles and sealed with a child-resistant closure. CFI-400945 tablets should be stored at ambient temperature (15-30°C).

Route of Administration:
CFI-400945 is taken orally at least 1 hour before, and 2 hours after, any food.

3.2 Durvalumab

See the current durvalumab product monograph for additional details and the most up to date information.

3.2.1 *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).

3.2.2 *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).

3.2.3 *Clinical Trials*

As of the most recent Investigator's Brochure, over 6000 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.

3.2.4 *Justification of Dose Selection*

Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W is planned. Fixed dosing of durvalumab is recommended only for subjects with > 30kg 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 (20mg/kg) dosing schedule. This is not expected to be applicable to this trial in an adult patient population.

3.2.5 *Pharmaceutical Data*

Supplied:
Please see the Pharmacy Manual. Durvalumab will be supplied by AstraZeneca/MedImmune as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab. The nominal fill volume is 10.0 mL.

Storage:
Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

Route of Administration:
Intravenous.

4.0 STUDY POPULATION

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

4.1 Eligibility Criteria

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 and to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar disease(s).

These eligibility criteria are expected to be followed. Any proposed variance must be discussed with CCTG prior to patient enrollment.

4.1.1 Patients must have histologically and/or cytologically confirmed diagnosis of breast cancer, that is advanced/metastatic or unresectable, for which no curative therapy exists, and be negative for ER, PR and HER2 by ASCO/CAP criteria on the most recent sample. Patients with tumour with either low (< 10%) ER expression who are PR and HER2 negative, or ER and HER2 negative but with low PR (< 10%) may be enrolled after discussion and confirmation with CCTG.

4.1.2 Only female patients will be enrolled.

4.1.3 All patients must have a formalin fixed paraffin embedded tissue block (from primary or metastatic tumour) available and must have provided informed consent for the release of the block (see Section 12.1).

Biopsies are optional but strongly encouraged for patients with accessible disease suitable for biopsy. The timing of tumour biopsies for patients who provide informed consent and are willing is prior to treatment (after enrollment; patients with biopsies within 90 days of enrollment with available blocks do not need re-biopsy), and again in Cycle 3, Day 1-8. An additional biopsy at the time of progression in patients with clinical benefit (see Section 5) is also encouraged. Lesions planned for biopsy must not be the only target lesion.

4.1.4 Presence of clinically and/or radiologically documented disease. All radiology studies must be performed within 21 days prior to enrollment (within 28 days if negative).

All patients must have measurable disease as defined by RECIST 1.1. The criteria for defining measurable disease are as follows:

Chest x-ray	≥ 20 mm
CT scan (with slice thickness of 5 mm)	≥ 10 mm → longest diameter
Physical exam (using calipers)	≥ 10 mm
Lymph nodes by CT scan	≥ 15 mm → measured in short axis

4.1.5 Patients must be ≥ 18 years of age.

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

4.1.7 Patients must have a life expectancy of 3 months or longer.

4.1.8 *Laboratory Requirements*
(must be done within 7 days prior to enrollment)

Hematology	Absolute neutrophils	$\geq$ 1.5 x 10^9/L
	Platelets	$\geq$ 100 x 10^9/L
Chemistry	Bilirubin	$\leq$ 1.5 x ULN (upper limit of normal)*
	AST and ALT	$\leq$ 2.5 x ULN $\leq$ 4.0 x ULN if patient has liver metastases
	Serum creatinine *or*: Creatinine clearance**	$\leq$ 1.5 x ULN $\geq$ 50 mL/min

* If confirmed Gilbert's, eligible provided $\leq$ 3 x ULN.

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

Females: GFR = 1.04 x (140-age) x weight in kg / serum creatinine in μmol/L

4.1.9 Patients must be able to swallow oral medications and have no known gastrointestinal disorders that may interfere with absorption (such as malabsorption).

4.1.10 *Previous Therapy*

Chemotherapy:
Patients must have had at least 1 prior line of cytotoxic chemotherapy for breast cancer, in any setting, which must have included an anthracycline and a taxane (unless contraindicated). Select patients that have not received both anthracycline and taxane therapy may be considered eligible after discussion with CCTG. There is no limit to the number of prior chemotherapy regimens.

Other Systemic Therapy:
Patients may have received other therapies including endocrine therapy and/or targeted therapies (including CDK4/6 inhibitors and PARP inhibitors).

Patients may not have received prior immunotherapies of any kind, nor any agent targeting PLK4.

Patients must have recovered (to at least grade 0 or 1) from all reversible toxicity related to prior chemotherapy or systemic therapy and have adequate washout as follows:

Longest of one of the following:

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

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

Surgery:
Previous surgery is permitted provided that a minimum of 21 days (3 weeks) have elapsed between any major surgery and date of enrollment, and that wound healing has occurred.

4.1.11 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.

4.1.12 Patients must be accessible for treatment and follow-up. Patients enrolled 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 enrolled 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 and response assessment which may occur through the course of the trial.

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

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

Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (failure rate of < 1% per year) while on study and for 3 months after the last dose of CFI-400945 and durvalumab. Cessation of birth control after this point should be discussed with a responsible physician. See Section 9.3 for additional details.

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

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

4.2 Ineligibility Criteria

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

4.2.1 Patients with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for > 2 years and which do not require ongoing treatment.

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

- History of significant neurologic or psychiatric disorder which would impair the ability to obtain consent or limit compliance with study requirements.
- Active infection requiring systemic therapy; (including any patient known to have active hepatitis B, hepatitis C or human immunodeficiency virus (HIV) or tuberculosis or any infection requiring systemic therapy).
- Active peptic ulcer disease or gastritis.
- Known pneumonitis or pulmonary fibrosis with clinically significant impairment of pulmonary function.
- Patients with diabetes mellitus are eligible but must be clinically stable on therapy (if applicable) and investigator and patient should be aware of the potential risk of immune mediated pancreatic toxicity and B cell destruction.

4.2.3 Patients are not eligible if they have a known hypersensitivity to the study drug(s) or their components.

4.2.4 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%.

4.2.5 Patients may not receive concurrent treatment with other anti-cancer therapy (other than bone-targeted therapy, if already taking and stable) or investigational agents while on protocol therapy.

4.2.6 Patients who have received growth factors within 28 days prior to initiation of dosing of CFI-400945 or who will require treatment with growth factors throughout the duration of the trial.

4.2.7 Pregnant or breastfeeding women.

4.2.8 Patients being treated with drugs listed in Appendix VI Table 1 are excluded. Patients being treated with drugs listed in Appendix VI Table 2 may be enrolled, but should be monitored carefully for toxicities resulting from potential interactions between CFI-400945 and these drugs. In addition, patients must avoid consumption of the fruit or juice of Seville oranges (e.g. marmalade), grapefruit, pomelos and star fruit from 7 days before the first dose of study drug and during the entire study due to potential CYP3A4 interaction with the study drug. Regular orange juice is allowed.

4.2.9 Patients with history of central nervous system metastases or spinal cord compression unless they have received definitive treatment, are clinically stable and do not require corticosteroids.

4.2.10 Patients with any medical condition that would impair the administration of oral agents including significant bowel resection, inflammatory bowel disease or uncontrolled nausea or vomiting.

4.2.11 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.

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

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

4.2.13 Live attenuated vaccination administered within 30 days prior to enrollment or within 30 days of receiving durvalumab.

4.2.14 Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA4.

4.2.15 Patients being treated with full dose warfarin. Patients with history of deep vein thrombosis or pulmonary embolus who are being treated with therapeutic doses of low molecular weight heparin, direct factor Xa inhibitors or prophylactic dose anticoagulants may be enrolled.

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 enrollment)	Biweekly cycles 1 and 2 and then Weekly	Day 1 each cycle, and as clinically indicated	Every 8 weeks	4 weeks after end of last cycle date	3 monthly follow-up (only required for pts without PD and ongoing toxicities[1]) then every 6 months until death
History and Physical Exam*						
Including: height[2] and weight, ECOG performance status, documentation of all measurable and non-measurable disease, clinical tumour measurements (if applicable); Vital signs: blood pressure, heart rate, temperature	X		X		X	
Laboratory Procedures/Assessments*						
CBC (neutrophils, platelets)	X	X[3]			X[4]	X[4]
PTT, PT/INR	X					
Serum creatinine[5], calcium, magnesium, phosphate, bilirubin, ALP, AST, ALT, LDH, albumin, glucose, amylase/lipase[6]	X		X		X[4]	X[4]
TSH[7]	X		X		X[4]	X[4]
Pregnancy Test[8]	X		X[9]			
Urinalysis	X[10]					
Radiology						
Tumour Imaging (Chest/upper abdomen CT scan; bone scan[11]; other scans as necessary to document disease)[12]	X[13] (within 21 days prior to enrollment or 28 days if negative)			X	X[14]	X[14]
Other Investigations						
EKG	X					
LVEF	X[10]					
Archival Tumour Tissue	X[15]					
Correlative Studies Blood Sampling	X[16]	See Section 12.0 for details				
Tumour biopsies	X[17]	X[17]				
Patient Drug Administration Diary (CFI-400945)		Each cycle				
Adverse events	X	Continuously			X[1]	

Footnotes on next page ...

*	Pre-treatment blood draws and physical exams may be done up to two working days 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
1	Adverse events felt to be related to protocol therapy will be followed until resolved to ≤ Grade 2. Reversible durvalumab- related adverse events ≥ grade 3 should be followed until resolved to baseline grade including related toxicity that occurs in the follow up period. Irreversible events may not need to be followed. Contact CCTG to discuss. Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0) (see Appendix V).
2	Height is only required at baseline.
3	Hematology is to be done twice weekly cycles 1 and 2. Provided patient has not experienced grade 3 or 4 neutropenia, hematology can be done weekly cycle 3 onward. For patients on for 6+ cycles, contact CCTG for a waiver if appropriate. See section 7 for additional monitoring of patients with toxicity.
4	Required at 4 weeks. To be done additionally every 3 months thereafter to follow abnormal lab results felt related until resolved to ≤ Grade 2.
5	If creatinine > 1.5 x ULN, calculated CrCl is required and must meet eligibility criteria for re-treatment. For patients who have discontinued CFI-400945 and are continuing on durvalumab alone, criteria for creatinine clearance may be lower. Please contact CCTG to discuss.
6	Required at baseline then as clinically indicated. 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.
7	Free T3 and free T4 will be measured if TSH is abnormal.
8	For women of childbearing potential only (urine or serum test). Within 72 hours prior to enrollment. Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.
9	As clinically indicated in WOCBP.
10	Required at baseline then as clinically indicated.
11	Bone scan is required at baseline for all patients. Thereafter, bone scan is only required to be repeated if positive at baseline to confirm CR/iCR, PR/iPR or SD/iSD, and/or when PD is suspected and as clinically indicated.
12	To ensure comparability, baseline scans and subsequent scans to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Maintain schedule every 8 weeks, even if cycles are delayed.
13	In order to evaluate tumour growth rate, if additional imaging was done prior to baseline radiology (done 3-12 weeks prior to Baseline scan), scans should also be evaluated according to RECIST 1.1 criteria and submitted with baseline reports. Note selection of target and/or non-target lesions is based on baseline imaging only. The same lesions (target and/or non-target) selected on baseline imaging should then be assessed on the pre-baseline scans if present.
14	To be done every three months until relapse or progression (iCPD), for patients with CR/iCR, PR/iPR, SD/iSD response as defined in Section 8.0. 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.
15	Must be confirmed available prior to enrollment on ALL patients. See Section 12.0 for details.
16	After enrollment but before the first dose of study treatment. Please refer to Section 12 and the Correlative Studies Manual for details regarding collection.
17	Optional paired biopsies should be obtained after enrollment (unless biopsy with available block within 90 days of enrollment) but prior to first dose and Cycle 3 (D1-8). Biopsies are also strongly recommended in all consenting patients when radiological disease progression on therapy is confirmed among patients who had initial response of CR/iCR, PR/iPR or SD/iSD greater than 4 months. See Section 12.1 for details.

5.1 Follow-up for Ineligible Patients

The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report and 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/ENROLLMENT PROCEDURES

6.1 Entry Procedures

All enrollments 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 enrolling patients will be provided at the time of study activation and will also be included in the "EDC Generic Data Management Guidebook", posted on the IND.239 trial specific web-site. If sites experience difficulties accessing the system and/or enrolling patients please contact the help desk (link in EDC) or the IND.239 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.239)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- tissue banking/optional consent version date
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values
- height and weight

6.2 Study Enrollment

Enrollment will be provided electronically.

At the time of enrollment, 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 enrollment.

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 enrollment.

All 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.

6.3 Inclusion of Women and Minorities

This trial will only enroll women. Men are excluded because the historical comparison cohort used to benchmark the response rate from this study included only one male patient. There are no exclusions based on race or ethnicity in this trial. This study, however, will be presented to patients through the major cancer-treatment institutions of the Canadian provinces, to which all racial/ethnic groups have equal access. The intention, therefore, is to recruit subjects from racial/ethnic groups in close approximation to the incidence of the disease in these groups.

7.0 TREATMENT PLAN

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

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

7.1 Treatment Plan

No pharmacokinetic or pharmacodynamic interaction is expected to occur and given the non-overlapping toxicity profiles, no formal dose escalation phase will occur. A safety review after the enrollment of 6 patients, who received at least 1 cycle and up to 3 cycles, will be conducted prior to reopening to further accrual. If needed, the starting dose of CFI-400945 will be reduced by one dose level.

7.1.1 *Drug Administration*

Cycle	Agent(s)	Dose	Route	Duration	Schedule	Cycle duration (days)
1	CFI-400945	32 mg	Oral	-	Days 1-7 then Days 15-21	28
2 onwards				-	Daily*	28
2 onwards	Durvalumab	1500 mg	IV	60 min	Day 1	28
* *An intermittent schedule may be used (see 7.1.3).*						

Cycle 1 will consist of CFI-400945 administered at the starting dose on a one week on and one week off schedule.

Depending on the toxicity observed in Cycle 1, Cycle 2 Day 1 will begin with durvalumab administration and CFI-400945 at either 32 mg continuously or on an intermittent schedule (Section 7.1.3 Table 1) continuously in subsequent 28-day repeating treatment cycles. Patients who experience no myelosuppression in 2 consecutive cycles may have CFI-400945 dose escalated to 40 mg (see 7.1.3). Patients may have the CFI-400945 dose reduced at any time due to toxicity. If either agent is held for toxicity, the other agent should also be held unless the toxicity is neutropenia alone.

Patients will take CFI-400945 by mouth at least 1 hour before, and 2 hours after, any food and should be encouraged to take the CFI-400945 at the same time each day at the time they find most convenient and are least likely to forget. On days when both CFI-400945 and durvalumab are administered, the timing of durvalumab administration in relation to CFI-400945 is not important, as long as they are started on the same day.

7.1.2 *Premedication*

No routine premedication (e.g. for nausea) or prophylaxis for hypersensitivity is required. For durvalumab, 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 *Dose Levels*

The following are dose levels for CFI-400945, which will be titrated according to the degree of toxicity:

DL+1 (escalation)	DL1	DL-1	DL-2
40 mg daily	32 mg daily	32 mg / 5 days per week (5 days on/2 days off)	32 mg / 3 days per week
Note: intermediate dose levels/schedules may be selected after review of data by CCTG and investigators.			

Durvalumab will be administered as a flat dose of 1500 mg for patients > 30 kg in weight. If patient weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be administered. No dose reductions are planned.

7.1.4 *Patient Monitoring*

Patients will be monitored before, during infusion and after the infusion of durvalumab. A 1-hour observation period is recommended after the first durvalumab infusion period. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent observation periods can be at the discretion of the investigator (30 minutes is suggested).

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.

7.1.5 *Dose Modifications – CFI-400945*

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V).

Reported and/or expected toxicities include, but are not limited to: amylase/lipase increases, neutropenia and leucopenia, febrile neutropenia fever and chills, infection, typhlitis/diarrhea, fatigue, increased liver function tests, nausea, vomiting, mucositis. The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.Doses should only be modified for toxicity related to CFI-400945.

Diarrhea > Grade 1 is not a common toxicity of CFI-400945. Patients who experience diarrhea should be carefully evaluated for possible immune mediated colitis and managed accordingly.

Following any interruption of dosing for toxicity as described below, CFI-400945 should not be re-started until ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L and resolution of all drug related toxicity to ≤ grade 2.

Table 1. Guidelines for CFI-400945 Dose Modifications for Neutropenia:

ANC (for dosing during cycle AND worst in prior cycle)	**Cycles**	**Dose and management[1, 3, 4]**
≥ 1.5 x10^9/L	All	No change. Note: If ≥ 1.5 x10^9/L for cycles 2 and 3 (or any 2 cycles after cycle 1) despite continuous oral dosing and having received at least 90% of planned doses[2]: may escalate 1 DL
1.0 x10^9/L- <1.5 x10^9/L	All	Hold[4] until ≥ 1.5 x10^9/L. No change in dose for next cycle.
Inability to receive at least 75% of planned dose within prior cycle	All	Hold[4] until ≥ 1.5 x10^9/L. Reduce 1 DL
<1.0 x10^9/L (with no fever) <5 days [5]		
<1.0 x10^9/L ≥ 5 days or febrile neutropenia	Cycle 1	Discontinue[6]
	Other cycles	Hold[4] until ≥ 1.5 x10^9/L. Reduce 2 DL

1. Hold if ANC < 1.5 x10^9/L; do not restart or start next cycle until ANC ≥ 1.5x10^9/L.
2. May also re-escalate after a prior dose reduction providing no febrile neutropenia and growth factors were not required and same conditions are met.
3. If Grade 3 or 4 ANC, CBC monitoring is required twice weekly for at least one full cycle after last event.
4. From Cycle 3 onward, CCTG may be contacted for an exemption to continue dosing if ANC ≥ 1.2 x10^9/L. If cannot restart dosing within 21 days, discontinue.
5. If grade 3 neutropenia occurs in Cycle 3 onwards, contact CCTG to discuss option of no DL reduction.
6. Consult CCTG for clarification for borderline values in asymptomatic patients.

Table 2. Guidelines for CFI-400945 Dose Modifications for Other Toxicity

Worst Toxicity	Management/Action	Dose of CFI-4000945 when re-started*
Hematologic		
Grade 1 or 2 thrombocytopenia	No action. If grade 2, increase surveillance with twice weekly CBC for 2 cycles provided no further dose modification needed	No change
Grade 3 thrombocytopenia	Hold until ≥ 100 x 10^9/L	Reduce by 1 DL AND increase surveillance with twice weekly CBC for at least 2 cycles
Thrombocytopenic bleeding	Hold and treat, increase surveillance with twice weekly CBC	Reduce by 2 DL or discontinue, AND increase surveillance with twice weekly CBC for at least 2 cycles
Non-Hematologic**		
Grade 2 AST and/or ALT AND Grade 2 bilirubin	Discontinue	Discontinue
Hy's Law (AST or ALT ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN)	Discontinue	Discontinue
Diarrhea Grade 2	Hold until immune mediated diarrhea excluded (or treated) and until recovered to ≤ grade 1	Restart without dose reduction
Other Grade 3	Hold until ≤ grade 2	Reduce by 1 DL
Other Grade 4	Discontinue	Discontinue

* If CFI-400945 cannot be restarted within 21 days, discontinue permanently.
** Despite adequate supportive care.

7.1.6 *Dose Adjustments – Durvalumab*

The major toxic effects of durvalumab 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 leading to T-cell activation and proliferation. Potential immune related AEs across the class 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.

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 durvalumab- related 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 4.1.8 are met and resolution of drug related toxicity, as detailed in Appendix II. For patients who have discontinued CFI-400945 and are continuing on durvalumab alone, criteria for creatinine clearance may be lower*. Please contact CCTG to discuss.

* For patients with low platelet counts that are not believed to be related for durvalumab please contact CCTG to discuss.

7.1.7 *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 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 are recommended:

- Patient evaluation to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
- Symptomatic and topical therapy should be considered for low-grade events.
- For persistent (greater than 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.

7.1.8 *Management of Infusion Reactions*

Guidelines for management of infusion-related reaction are summarized in Appendix II. The standard infusion time for durvalumab is 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.

7.1.9 *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.

7.1.10 *Duration of Therapy*

Treatment will continue until the criteria for removal from protocol treatment have been met (see Section 10).

7.1.11 *Patient Compliance*

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

7.2 Concomitant Therapy

7.2.1 *Permitted*

- Other supportive and palliative care (e.g. pain control) as required throughout the study.
- Bone-targeted therapy for patients with bone metastases (bisphosphonates or denosumab).
- Anti-emetics or anti-diarrheal agents as required.
- 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 or prophylactically. Please consult CCTG in the case of patients experiencing multiple delays/omissions as exceptions may be made for patients who are benefitting from protocol therapy.

7.2.2 *Not Permitted*

- Administration of any other anti-cancer therapy is not permitted while the patient is receiving protocol therapy. Thereafter, patients may be treated at the investigator's discretion.
- 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.)
- Cytokines.
- Corticosteroids IV or PO (except for the treatment of ≥ grade 3 infusion reaction, or treatment-related toxicity (See Appendix II). Note: Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed, as are oral dose of steroids equivalent to 10 mg or less of prednisone.
- 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
- Drugs listed in Appendix VI Table 1 are not permitted during the study. Drugs listed in Appendix VI Table 2 should be used with caution only when it is absolutely necessary.

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 *[Eisenhauer 2009]*.

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

8.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as the Immune-Related modified RECIST. Investigators should continue treatment, as appropriate, in the absence of unacceptable toxicity, until unequivocal disease progression. This is particularly important for patients in whom pseudoprogression may have occurred. Follow up response assessments must be continued until unequivocal disease progression has occurred.

8.2.1 *Measurable Disease*

Measurable *tumour lesions* 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 < 10mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Eisenhauer 2009]*) before CR can be accepted. Confirmation of response is required.

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.

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) ANDan 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.

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.

* For this study, baseline is defined as the date of enrollment.

** Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see Table 2.

For non randomized trials, where confirmation of response is required, best overall response can be interpreted as follows:

Response: First Time Point	Subsequent Time Point	BEST Overall Response	Also Requires
CR	CR	CR	Normalization of tumour markers, tumour nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	
* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.			

8.3 Immune-Related Response Assessment

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

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

Confirming Progression

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

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

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum:

- Continued unequivocal progression in non-target disease with an increase in tumour burden;
- Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.

- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

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

New Lesions

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

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

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

Table 2: Time-point (TP) iResponse

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

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

Table 3: iRECIST Best Overall Response (iBOR)

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

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

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

8.4 Response Duration (RECIST 1.1 and iRECIST)

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

8.5 Stable Disease Duration

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

8.6 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, 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 ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.6.2 *Chest X-ray*

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

8.6.3 *CT, MRI*

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

8.6.4 *Ultrasound*

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

8.6.5 *Endoscopy, Laparoscopy*

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

8.6.6 *Tumour Markers*

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

8.6.7 *Cytology, Histology*

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

9.0 SERIOUS ADVERSE EVENT REPORTING

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

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' 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 fulfil 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.239 section of the CCTG website (www.ctg.queensu.ca).

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

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.239 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.239 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

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

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.14.

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®)**	• "Implants": Etonogestrel-releasing implants: e.g. Implanon® or Norplan® • "Intravaginal Devices": Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • "Injection": Medroxyprogesterone injection: e.g. Depo-Provera® • "Combined Pill": Normal and low dose combined oral contraceptive pill • "Patch": Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • "Minipill***": Progesterone based oral contraceptive pill using desogestrel e.g. Cerazette®
* Highly effective (i.e. failure rate of <1% per year). ** This is also considered a hormonal method. *** Cerazette® is currently the only highly effective progesterone based pill.	

9.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants. Pregnancies occurring up to 3 months after the completion of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage, under the "Toolbox" link.

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 participants, if required by local policy, a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

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

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

9.3.3 *Exposure Reporting (Non-study Participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure using the CCTG Exposure Reporting Form available from the trial webpage, under the "Toolbox" link.

Once informed consent has been obtained, the form should be updated to provide furtherexposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual for a duration of 30 days. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also 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 exposure results in death; 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 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 serious adverse events within 1 working day of receipt by 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 Reporting Responsibility to UHN

UHN will be notified of all serious adverse events related to CFI-400945 within 1 working day of receipt by CCTG.

9.7 UHN and AstraZeneca Reporting Responsibilities

UHN and AstraZeneca shall notify CCTG of individual safety reports from other studies using CFI-400945 and durvalumab respectively, which may affect the overall safety profile of the study and which they have reported to Health Canada. In addition, UHN and AstraZeneca will provide 3 monthly line listings to CCTG for all other reports.

9.8 Reporting Serious Adverse Events 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.239 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.239 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.
- Tumour progression or disease recurrence as defined in Section 8.0.
- Request by the patient.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Duration of Protocol Treatment

(see Section 8.0 for response definition)

- Treatment with will continue until progression in the absence of unacceptable toxicity (Section 7).
- Patients who progress (treatment failure) will go off study at the time progression is documented clinically and/or radiographically by RECIST 1.1 and iRECIST as appropriate.
- Patients who discontinue one protocol therapy for toxicity may continue the other protocol therapy until progression in the absence of unacceptable toxicity.

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 CR/iCR, PR/iPR, or SD/iSD ongoing, follow-up will be required every 3 months until relapse (see Section 5.0 for investigations to be performed).

Continued follow up after progression (on treatment or during follow up), using an abbreviated form (including subsequent therapies) every 6 months is required until CCTG advises centres that the final analysis has been performed and follow up can be discontinued.

If patient is unable to return to participating centre for follow up, please contact CCTG to discuss possible options prior to considering 'withdrawal of consent' processes. Remote oversight allowing data submission may be feasible.

Death report will be required on all patient unless advised by CCTG. 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

As part of the trial, copies of x-rays and/or scans may be collected to evaluate cancer response to treatment. There will be no central radiology review for this study.

11.3 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

Collection and immediate shipment of time sensitive samples (e.g. cfDNA) MUST occur after enrollment. This is to ensure that the samples shipped to the Tumour Bank have a CCTG patient ID, which is required, in order to track and catalogue specimens.

A detailed Correlative Studies Manual will be provided on the IND.239 trial specific website, which will include details regarding sample preparation, handling and shipping.

Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of enrollment to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

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

Genetic Testing

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

As all biomarker testing done for this study will be conducted in a research laboratory, the results are not validated. There are no plans to return results to patients.

12.1 Protocol-Mandated Correlative Studies

Tumour Tissue Collection - Archival

The submission of a representative block of the diagnostic tumour tissue is mandatory for participation in this trial. One tumour block and one adjacent normal tissue block are requested from all of the biopsies or resections of the breast tumour.

If no primary cancer blocks are available, one block of metastatic tissue can be sent alone. Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to enrollment of the first patient to allow cores (two 2 mm cores of tumour from the block) and a predetermined number of slides of representative tumour tissue to be substituted in response to the Central Tumour Bank request.

Tumour Tissue Collection (Serial Paired Samples)

Biopsies are optional but strongly encouraged for patients with accessible disease suitable for biopsy. Optional biopsies may be performed at baseline (after enrollment, prior to treatment; patients with biopsies within 90 days of enrollment with available blocks do not need re-biopsy), and between Cycle 3 Day 1 and 8 (contact CCTG if unable to schedule within this time period). An additional optional biopsy is strongly recommended for all consenting patients when radiological disease progression on therapy is confirmed among patients who had initial response of CR/iCR, PR/iPR or SD/iSD greater than 4 months.

Blood Collection

The CCTG is interested in exploring the use of surrogate tissues such as blood, serum and plasma in evaluating potential prognostic or predictive biomarkers, or as evidence of pharmacodynamics effects. Mandatory samples will be collected for circulating free DNA (cfDNA) at baseline, C3D1, C5D1, C7D1 and at progression (iUPD; will need to be repeated after initial iUPD if the patient has a subsequent response, followed by iUPD again). Samples will be collected to measure dynamic changes in levels of tumour-derived DNA in plasma with study treatment.

Planned Assays on Tissue

Molecular analyses including but not limited to next-generation DNA/RNA sequencing and immunohistochemistry will be performed on archival and recent tumour (or normal tissue) materials to identify potential biomarkers of response, histologically assess centrosomes and aberrant mitoses, and evaluate genomic alterations and other molecular features (i.e. gene or protein expression levels).

13.0 STATISTICAL CONSIDERATIONS

This is an open label multicentre phase II trial to evaluate the anti-tumour activity of CFI-400945 when given with durvalumab by determining the objective response rate in patients as defined in Section 4.1.1. A 2-stage Simon minimax design will be used.

13.1 Primary Endpoints and Analysis

The primary endpoint of this study is objective response rate, which will be estimated by the proportion of evaluable patients who had complete response (CR) or partial response (PR) as their best response as assessed by RECIST 1.1 criteria. The exact 95% confidence interval for the response rate will be calculated. The median and range of the duration of response, defined as the time from date of CR or PR to the date when progression or death is observed, will be estimated based on Kaplan-Meier method.

Secondary objectives include Disease Control Rate (DCR, defined as CR or PR or stable disease (SD) > 16 weeks in duration) which will be analyzed similarly as objective response rate, as well as response rate determined by iRECIST.

13.2 Sample Size and Duration of Study

A 2-stage Simon minimax design will be used.

For sample size estimation, a response rate of 0.15 to monotherapy is assumed. The null hypothesis that the true response rate is 15% or less will be tested against a one-sided alternative. In the first stage, 15 patients will be accrued. If 2 or less responses are observed, the study will be stopped. Otherwise, accrual will continue to a total of 28. The null hypothesis will be rejected if 8 or more responses are observed in 28 patients. This design yields a type I error rate of 5% and power of 0.8 when the true response rate is 35%.

13.3 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported semi-annually at investigators' meetings. A safety review after the enrollment of 6 patients, who have received at least 1 cycle and up to 3 cycles, will be conducted prior to reopening to further accrual.

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 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 supported and coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions). Research supported by AstraZeneca and University Health Network."

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair/s 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 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 Exposure Reporting*

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

The trial-specific consent form for "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the 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 exposure.

Obtaining Consent for Research on Children

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

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

15.4 Discontinuation of the Trial

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

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

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

15.5 Retention of Patient Records and Study Files

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

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

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

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

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

15.6 Centre Performance Monitoring

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

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

15.7 On-Site Monitoring/Auditing

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

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

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

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

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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

General

Details of Drug Distribution, Supply and Control/Accountability are provided in the *IND.239 Pharmacy Information Manual*, available on the IND.239 website (http://www.ctg.queensu.ca/trials/.html).

Distribution

CFI-400945 and durvalumab will be supplied to the CCTG distributor, Bay Area Research Logistics (BARL) and distributed by BARL to participating sites in Canada.

Investigational product should be stored in a secure area according to local regulations and under the storage conditions stipulated on the investigational product label

Resupply

For re-supply of CFI-400945 and durvalumab, sites should print off and submit a Drug Re-Supply Form available on the IND.239 website. This form should be submitted directly to BARL. Once received, BARL will process the request and initiate shipment of re-supply. Sites should allow for 5-7 working days for shipment to arrive.

Drug Accountability

The investigational products are to be prescribed only by the Qualified Investigator or 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 utilizing the Drug Accountability Log, available on the IND.239 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 and confirmed with CCTG. 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 and confirmed with CCTG. Documentation of destruction must be kept on file in the site pharmacy and is subject to on site monitoring/audit.

Drug Destruction of Unused Medication (End of Trial)

Instructions for return or destruction of unused drug will be supplied at the time of expiry and at trial closure.

** PLEASE NOTE **
DRUG FROM THIS SUPPLY IS TO BE USED
ONLY FOR PATIENTS ENROLLED 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 enrollment 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 electronic Case Report Forms (eCRFs), please refer to the Data Management Guidebook available on the IND.239 web-site (www.ctg.queensu.ca).

This trial will use a web-based Supporting Document Upload Tool for collection of supporting documentation. Supporting Documents are required to be uploaded immediately after the report they refer to has been submitted electronically).

The ELECTRONIC CRFs to be used in this trial are:

Electronic Case Report Form	To be Completed/Submitted Electronically:	Supporting Documentation*	
		Mandatory Submission: To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request: To be uploaded immediately after request
BASELINE REPORT	Due within 2 weeks of patient enrollment.	Signature page of main and optional consent forms; diagnostic pathology, protocol-mandated baseline radiology and tumour measurement sheet (TMS)	ECG, LVEF, additional clinical, laboratory or imaging reports that may impact on decision regarding eligibility
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.	Radiology reports for protocol-mandated imaging and non-protocol mandated imaging, if relevant to disease assessment, TMS	Patient drug administration diary, additional clinical, laboratory or imaging reports that may inform evaluation of safety
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 going off protocol treatment. Due within 2 weeks after contact with patient.	Radiology reports for protocol-mandated imaging and non-protocol mandated imaging, if relevant to disease assessment, TMS	Additional clinical, laboratory or imaging reports that may inform evaluation of safety
FOLLOW-UP REPORT	To be completed every 3 months or 6 months (see Section 5.0 and 10.4). Due within 2 weeks after contact with patient.	Radiology reports for protocol-mandated imaging and non-protocol mandated imaging, if relevant to disease assessment, TMS	Additional clinical, laboratory or imaging reports that may inform evaluation of safety
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.		
DEATH REPORT**	Required for all patients unless advised by CCTG. Due within 2 weeks of knowledge of death.	Autopsy report, if done.	Additional clinical, laboratory or imaging reports that may inform evaluation of cause of death
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.		Additional clinical, laboratory or imaging reports that may inform evaluation of safety including admission and discharge summaries/notes

footnotes on next page ...

* Scan and upload in the EDC Supporting Document Upload Tool (SDUT) - please refer to the slide set on the IND.239 website for guidance. Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) as not submitted. All patient identifiers, other than the CCTG patient ID assigned at enrollment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements. Acceptable methods include:

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

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

** 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 5.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX VI - PROHIBITED MEDICATIONS

Table 1. Drugs to be Excluded

Alfentanil	Pimozide
Cyclosporine	Quinidine
Digoxin	Sirolimus
Dihydroergotamine	Tacrolimus
Ergotamine	Tizanidine
Fentanyl	Theophylline
Mephenytoin	Warfarin
Phenytoin	

Table 2. Drugs to be Used With Caution

Alosetron	Felodipine	Quetiapine
Aprepitant	Fluticasone	Ramelteon
Budesonide	Indinavir	Saquinavir
Buspirone	Lansoprazole	Sildenafil
Caffeine	Lopinavir	Simvastatin
Duloxetine	Lovastatin	Tacrine
Conivaptan	Lurasidone	Tiprinavir
Darifenacin	Maraviroc	Tolvaptan
Darunavir	Melatonin	Triazolam
Dronedarone	Midazolam	Vardenafil
Eletriptan	Nisoldipine	
Eplerenone	Omeprazole	

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 ENROLLMENT

All patients must be enrolled 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)	Caitlin Burns Study Coordinator, CCTG Email: cburns@ctg.queensu.ca or: Dr. Lesley Seymour Senior Investigator, CCTG Email: lseymour@ctg.queensu.ca or: Dr. Pierre Olivier Gaudreau Senior Investigator, CCTG Email: p-ogaudreau@ctg.queensu.ca		
STUDY CO-CHAIRS	Dr. David Cescon Study Co-Chair or: Dr. Andrew Robinson Study Co-Chair	Contact CCTG	Contact CCTG
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Lesley Seymour Senior Investigator, CCTG or: Dr. Pierre Olivier Gaudreau Senior Investigator, CCTG or: Caitlin Burns Study Coordinator, CCTG	613-533-6430	613-533-2411
DRUG ORDERING See Appendix III for full details.	See Appendix III and trial website: http://www.ctg.queensu.ca		