PROTOCOL DATE: 2016-JUL-20
CCTG TRIAL: PA.7

HEALTH CANADA SUBMISSION

AMENDMENT #2: 2018-MAR-20

CANADIAN CANCER TRIALS GROUP (CCTG)

A RANDOMIZED PHASE II TRIAL OF GEMCITABINE AND NAB-PACLITAXEL VS. GEMCITABINE, NAB-PACLITAXEL, DURVALUMAB AND TREMELIMUMAB AS 1ST LINE THERAPY IN METASTATIC PANCREATIC ADENOCARCINOMA

CCTG Protocol Number: **PA.7**

STUDY CHAIR:	Daniel Renouf
TRIAL COMMITTEE:	Derek Jonker Petr Kavan Neesha Dhani
SENIOR INVESTIGATOR:	Chris O'Callaghan
BIOSTATISTICIAN:	Dongsheng Tu
QUALITY OF LIFE COORDINATOR:	Alice Wei
PATHOLOGY COORDINATOR:	David Schaeffer
STUDY COORDINATORS:	Barbara Graham Lisa Gallinaro
REGULATORY SPONSOR:	CCTG
SUPPORTED BY:	AstraZeneca

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

TABLE OF CONTENTS

STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to CCTG and AstraZeneca

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, 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 AstraZeneca and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to AstraZeneca and CCTG of any such disclosure.

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

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

_____ _____

Qualified Investigator
(printed name and signature)

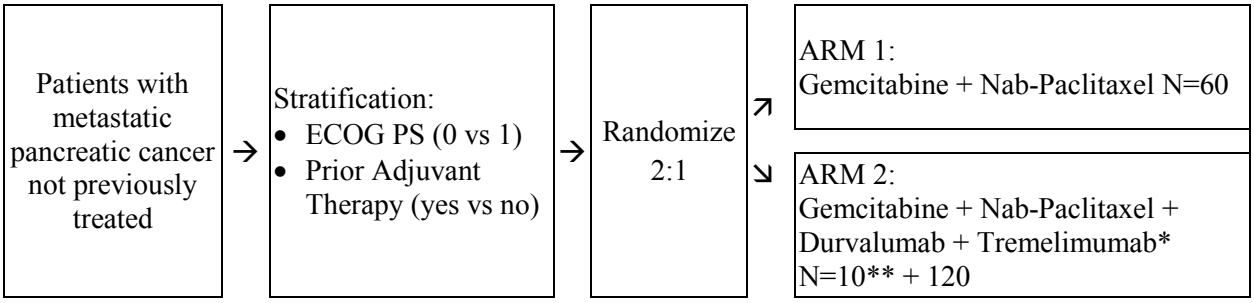
Date

Protocol Number: CCTG PA.7

CENTRE: _____

TREATMENT SCHEMA

This is a multi-centre, phase II study of doublet immunotherapy (durvalumab + tremelimumab) in combination with standard chemotherapy regimens (gemcitabine and nab-paclitaxel) *versus* standard chemotherapy in patients with newly diagnosed, untreated, metastatic pancreatic adenocarcinoma.



Primary Endpoint: Overall Survival

* *Tremelimumab and Durvalumab q28 days for 4 cycles, followed by Durvalumab monotherapy until objective progression.*

** *Prior to the randomized component, 10 patients will first be accrued to ensure safety and tolerability of the combination of gemcitabine + nab-paclitaxel + durvalumab + tremelimumab.*

1.0 OBJECTIVES

Ten patients will be enrolled initially to Arm 2 to confirm the safety and tolerability of the combination of gemcitabine + nab-paclitaxel + durvalumab + tremelimumab.

1.1 Primary Objective

The primary objective is to determine the effect on overall survival (OS), of the addition of a durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.

1.2 Secondary Objectives

- To determine the effect on progression free survival (PFS) of the addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.
- To assess the toxicity and safety of durvalumab + tremelimumab in combination with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.
- To determine the effect on objective response rate (ORR) of the addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.

1.3 Tertiary Objectives

- To determine the effect on quality of life (QoL) of the addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.
- To determine the effect of tumour PD-L1 expression assessed by IHC on efficacy of the addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.
- To determine the effect of tumour hENT/SPARC expression assessed by IHC on efficacy of the addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.
- To investigate tumour gene expression signatures associated with the response to the addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel in patients with metastatic pancreatic cancer.
- To assess sequential circulating tumour DNA in patients with metastatic pancreatic cancer receiving standard 1st line chemotherapy with gemcitabine/nab-paclitaxel + durvalumab + tremelimumab.

2.0 BACKGROUND INFORMATION AND RATIONALE

Pancreatic Cancer

Pancreatic cancer is the 4th leading cancer death (after lung, colorectal and breast), with 4800 new cases and 4600 deaths expected in Canada in 2015 *[Canadian Cancer Society Statistics 2015]*. This 96% case mortality ratio is the highest of any cancer. There are a number of causes of the high mortality rate of pancreatic cancer, including the lack of effective screening tests resulting in the majority of patients being diagnosed with advanced disease, and the general chemoresistance of this cancer. There has been recent progress in treatment options in the metastatic setting with data supporting the use of FOLFIRINOX or gemcitabine and nab-paclitaxel therapy as a 1st line treatment in patients with metastatic pancreatic cancer and a good performance status *[Conroy 2011, Von Hoff 2013]*. Despite these advances the majority of patients with metastatic pancreatic cancer will survive less than 1 year thus the development of more effective treatment strategies is a critical unmet need.

One strategy to target cancer that has recently shown significant anti-tumour activity in multiple tumour types is through modulation of the immune system. There has been significant progress in this field over the past several years, with immunomodulatory strategies now becoming standard of care in melanoma, non-small cell lung cancer, and renal cell carcinoma. Clinical trials assessing immunomodulatory strategies are underway in multiple other cancer types.

Immunotherapy & Immune Checkpoint Inhibitors

Immune responses directed against tumours are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumour types. In a number of these cancers, including lung *[Mu 2011]*, renal *[Thompson 2005; Thompson 2006; Krambeck 2007]*, pancreatic *[Nomi 2007; Loo 2008; Wang 2010]*, ovarian cancer *[Hamanishi 2007]*, and hematologic malignancies *[Andorsky 2011; Brusa 2013]*, tumour cell expression of PD-L1 is associated with reduced survival and an unfavourable prognosis.

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumours to help evade detection and elimination by the host immune system tumour response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell *[Keir 2008; Park 2010]*. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumour microenvironment, PD-L1 expressed on tumour cells binds to PD-1 and CD80 on activated T cells reaching the tumour. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumour from immune elimination *[Zou 2008]*.

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

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) also known as CD152 (cluster of differentiation 152) is another protein involved in T-cell activation. Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production *in vitro* in whole blood or peripheral blood mononuclear cell (PBMC) culture.

Durvalumab

Durvalumab is a novel IgG1-kappa PD-L1 inhibitor with potent and specific binding to PD-L1 at picomolar concentrations and has directed mutations in the Fc region, limiting off-target cytotoxicity in PD-L1-expressing immune cells *[Khleif 2013; Stewart 2011]*. Surrogate anti-PD-LI antibodies have been shown to increase T-cell activation *in vitro* by blocking PD-L1/PD-1 engagement and inducing antitumour responses in tumour-bearing mice, with corresponding changes in peripheral immune markers. Durvalumab has also been shown to inhibit tumour growth *in vivo* xenograft models

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). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that durvalumab inhibits tumour growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumour model when given as monotherapy and resulted in complete tumour regression in > 50% of treated mice when given in combination with chemotherapy.

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumours. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function. Durvalumab has potent and specific binding to PD-L1 at picomolar concentrations and has directed mutations in the Fc region, limiting off-target cytotoxicity in PD-L1-expressing immune cells *[Khleif 2013; Stewart 2011]*. Surrogate anti-PD-LI antibodies have been shown to increase T-cell activation in vitro by blocking PD-L1/PD-1 engagement and inducing antitumour responses in tumour-bearing mice, with corresponding changes in peripheral immune markers. Durvalumab has also been shown to inhibit tumour growth *in vivo* xenograft models.

Tremelimumab

Tremelimumab is a human IgG2 monoclonal antibody directed against the T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4) *[Tarhini 2013]*. CTLA-4 is a co-inhibitory receptor expressed on activated T cells and regulates early stage T cell activation, reducing the amplitude. Tremelimumab binds to CTLA4 and blocks the binding of the antigen-presenting cell ligands B7-1 and B7-2 to CTLA4, resulting in inhibition of B7-CTLA4-mediated downregulation of T-cell activation.

Tremelimumab is an IgG 2 kappa isotype mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) also known as CD152 (cluster of differentiation 152) this is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer.

CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumour activity in animal models, including killing of established murine solid tumours and induction of protective anti-tumour immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumour activity in patients with solid tumours.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cut-off date of 12 November 2014 (for all studies except D4190C00006, which has a cut-off date of 4 December 2014), 973 patients have received tremelimumab monotherapy (not including 497 patients who have been treated in the blinded phase IIb study, D4880C00003) and 208 patients have received tremelimumab in combination with other agents. Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22 days. Overall, a low incidence of ADAs (< 6%) was observed for treatment with tremelimumab.

Combination of Durvalumab and Tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity because the mechanisms of action of CTLA-4 and PD-1 are non-redundant *[Pardoll 2014]*; therefore, the use of durvalumab + tremelimumab combination therapy for the treatment of cancer is under concurrent investigation. In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable *[Wolchok 2014]*. Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC *[Antonia 2014a]*.
Study D4190C00006 is a phase Ib dose-escalation study to establish safety, PK/PDx, and preliminary anti-tumour activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

As of 20 February 2015, ADA data were available from 60 subjects for durvalumab and 53 subjects for tremelimumab in Study D4190C00006. Four of 60 subjects were ADA positive for anti-durvalumab antibodies post treatment. One of 53 subjects was ADA positive for anti-tremelimumab antibodies post treatment. There was no clear relationship between ADA and the dose of either durvalumab or tremelimumab, and no obvious association between ADA and safety or efficacy.

In order to reduce the dosing frequency of durvalumab to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety, and efficacy profile, cohorts were narrowed to 15 and 20 mg/kg durvalumab q4w. PK simulations from the durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUCss; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w durvalumab. The observed durvalumab PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of durvalumab 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median Cmax at steady state (Cmax,ss) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state (Ctrough,ss) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented PDx activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10 mg/kg and 20 mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥ 3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥ 3 AEs or treatment-related SAEs. No dose-limiting toxicities were reported.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15 and 20 mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR), 1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD). (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Additionally, of all cohorts, the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥ 3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

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

Rationale for combined chemotherapy and immune checkpoint inhibition

There is a significant degree of pre-clinical and early clinical data that immunomodulatory therapies may have activity in pancreatic adenocarcinoma. T-cell induction through CD40 agonists has shown promising activity in pre-clinical and early clinical studies *[Beatty 2011]*. A vaccine strategy of the GVAX vaccine in combination with CRS 207 (attenuated strain of Listeria expressing mesothelin) showed promising activity in a phase II study and a larger randomized phase II is currently underway *[Le 2015]*.Regarding the efficacy of checkpoint inhibitors, there is a paucity of data up to this point, with only data from 14 patients demonstrating objective responses to single agent anti-PDL-1 therapy *[Brahmer 2012]*.

One potential explanation for resistance to single agent PD-L1 inhibition may be related to the tumour microenvironment associated with pancreatic cancers, and specifically the role of cancer associated fibroblasts (CAFs). It is hypothesized that activity of single agent checkpoint inhibitor therapy in pancreatic cancer may be limited due to lack of epithelial activated T-cells, related to immune-inhibitory signals from the surrounding microenvironment, including signaling from CAFs. KPC mouse model studies have demonstrated that CAFs in the tumour stroma that are fibroblast associated protein expressing (FAP-positive) secrete CXCL12 leading to an immunosuppressive environment *[Feig 2013; Garrido-Laguna 2015]*.

A potential strategy to improve the sensitivity of checkpoint inhibitor therapy in pancreatic cancer is through the depletion of CAFs. KPC mouse model experiments whereby FAP-positive CAFs were depleted demonstrated greater sensitivity to PDL-1 inhibition. Depletion of CAFs has also been demonstrated to increase sensitivity to CTLA-4 inhibition *[Ozdemir 2014]*.

Gemcitabine and nab-paclitaxel is known to deplete stromal cells and CAFs *[Hidalgo 2013; Feig 2013; Alvarez 2013]*, thus the combination of gemcitabine and nab-paclitaxel may induced greater sensitivity to PDL-1 and CTLA-4 inhibition. Another potential mechanism of chemotherapy induced immune sensitization is through the release of neoantigens with tumour cell death *[Ma 2013]*. We hypothesize that the combination of chemotherapy with both anti-tumour and anti-stromal activity with immune checkpoint inhibition with result in a significant improvement in progression free survival and overall survival in metastatic pancreatic cancer compared to chemotherapy alone.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Durvalumab

3.1.1 *Name and Chemical Information*

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

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

3.1.2 *Chemical Structure*

Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

3.1.3 *Mechanism of Action*

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

3.1.4 *Experimental Antitumour Activity*

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

3.1.5 *Animal Toxicology*

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

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

3.1.6 *Clinical Trials*

As of the most recent Investigator's Brochure over 5000 subjects have been enrolled and treated in ongoing durvalumab clinical studies No studies have been 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 diarrhea/colitis, and intestinal perforation, pneumonitis/ILD, ALT/AST increases/hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity (e.g. Guillain-Barré syndrome, and myasthenia gravis), endocrinopathies (i.e. hypophysitis, hypopituitarism, adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus), rash/dermatitis, nephritis/blood creatinine increases, pancreatitis (or labs suggestive of pancreatititis – increased serum lipase, increase serum amylast), myocarditis and myocitis/polymositis. Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

3.1.7 *Pharmaceutical Data - Durvalumab*

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

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

Please refer to the PA.7 Pharmacy Manual for additional details.

3.2 Tremelimumab

3.2.1 *Name and Chemical Information*

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

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

3.2.2 *Chemical Structure*

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

3.2.3 *Mechanism of Action*

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

3.2.4 *Experimental Antitumour Activity*

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

3.2.5 *Clinical Trials*

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

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

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

3.2.6 *Pharmaceutical Data - Tremelimumab*

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

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

Route of Administration:
Intravenous.

Please refer to the PA.7 Pharmacy Manual for additional details.

3.3 Fixed Dosing in Durvalumab and Tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

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

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

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

Fixed dosing of durvalumab and tremelimumab is recommended only for subjects with > 30 kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule. This is not expected to be applicable to this trial in an adult patient population.

3.4 Gemcitabine

3.4.1 *Name and Chemical Information*

Gemcitabine (difluorodeoyxcytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in *in vivo* and *in vitro* tumours.

Chemical Name:	2'-Deoxy-2, 2'-Difluorocytidine monohydrochloride
Emperical Formula:	$C_9H_{12}CIF_2N_3O_4$
Molecular weight:	299.66
Appearance:	Crystalline powder
Colour:	White or off-white to translucent

3.4.2 *Mechanism of Action*

Gemcitabine (2'-2'-difluorodeoxycytidine; dFdC) is an analogue of deoxycytidine which, like ara-C (cytarabine), must be phosphorylated by cytidine deaminase into di- and tri-phosphate forms (dFdCDP and dFdCTP) to exert its cytotoxic effects of inhibition of DNA replication and repair. Gemcitabine was selected for clinical development because of the observation that, unlike ara-C, it exhibited marked antitumour effects in numerous murine and human xenograft solid tumour systems, including lung, breast, colon and ovarian cancer models. This differing spectrum of activity seems to be related to gemcitabine's prolonged intracellular retention; a property related to several mechanisms. These include the drug's ability to potentiate its own conversion into the phosphorylated form by decreasing intracellular deoxycytidine triphosphate (dCTP) levels with resulting enhanced kinase activity. The gemcitabine-induced fall in dCTP also decreases the activity of deoxycytidine monophosphate deaminase, which in turn helps maintain levels of phosphorylated drug. Thus the effect of the presence of activated gemcitabine (i.e. the phosphorylated form) is to decrease dCTP with resulting enhanced activity of those kinases responsible for gemcitabine activation and decreased activity of those deaminases responsible for elimination of the activated form of drug. These mechanisms are termed "self-potentiating".

3.4.3 *Experimental Antitumour Activity and Toxicity information*

Gemcitabine has been extensively evaluated in phase I, II, III studies and has a well characterized toxicity and efficacy profile. Gemcitabine has activity in a number of tumour types including pancreas, breast, bladder, lung, colon, head and neck and biliary tract cancer. It received FDA approval based on its activity and clinical benefit in pancreatic cancer *[Burris 1997]*. Preclinical studies show synergism with a number of drugs including 5-FU.

Pancreatic Cancer:

Data from two clinical trials evaluated the use of gemcitabine in patients with locally advanced or metastatic pancreatic cancer. The first trial compared gemcitabine to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of gemcitabine in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemcitabine was administered intravenously at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with gemcitabine. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

It is generally a well-tolerated drug even when given to frail and elderly patients. The most common toxicity is short-lived myelosuppression. Weekly single agent doses between 800-1250 mg/m^2 have been associated with the following grade 3, 4 hematologic toxicities (WHO classification): neutropenia 25%, anemia 8-11% and thrombocytopenia 5-7%. Discontinuation occurred in < 1% of patients (n=979). Non-hematologic toxicities are well tolerated and occur with the following frequencies: nausea and vomiting (mild to moderate with 17% requiring antiemetic therapy), diarrhea and stomatitis (mild, 13%), proteinuria and hematuria (mild, 33%). Hemolytic uremic syndrome has been reported in < 1%. A fine maculopapular rash has been reported in about 25% of patients; it is usually mild and responds to local therapy. Mild and transient elevations of transaminases (usually WHO grades 1 and 2) have been documented in about two thirds of patients with no evidence of increasing toxicity with longer treatment or cumulative dose. Fever is common (33% all grades); infection is not- 9% (grade 3 or 4: 1%). Flu-like symptoms regardless of cause occurred in about 19% of patients but discontinuation due to this cause is rare (< 1%). Serious cardiac toxicities are rarely reported and have tended to occur in patients with pre-existing cardiovascular disease. Pulmonary effects, sometimes severe (such as pulmonary edema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)), have been rarely reported and tend to occur in patients with underlying lung disease.

In the setting of organ dysfunction (hepatic and renal), there is more toxicity, in particular transient hepatic dysfunction. A phase I trial of gemcitabine in patients with organ dysfunction demonstrated significant but transient hyperbilirubinemia in patients with baseline elevations in bilirubin levels *[Venook 2000]*. Baseline elevated transaminases did not appear to be predictive of toxicity. Patients with renal dysfunction had increased but unpredictable toxicity. Dose reductions were recommended in the setting of elevated bilirubin and caution with renal insufficiency. In the phase II trial which evaluated patients with stable hepatic function, the combination did not result in significant toxicity.

3.4.4 *Pharmaceutical Data*

Supplied:
Commercial supply of gemcitabine will be used in this study. See label/package insert for additional information.

Route of Administration:
Gemcitabine is administered intravenously.

3.5 Nab-Paclitaxel

3.5.1 *Name and Chemical Information*

Proper name:	Paclitaxel
Chemical name:	5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine
Molecular formula:	C47H51NO14
Molecular mass:	853.91
Physicochemical properties:	Paclitaxel is a white to off-white crystalline powder. It is highly lipophilic, insoluble in water, and melts at approximately 216 to 217°C.

3.5.2 *Mechanism of Action*

Paclitaxel, the active pharmaceutical ingredient in nab-paclitaxel for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel), is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

3.5.3 *Experimental Antitumour Activity*

Nab-paclitaxel has is indicated for the treatment of metastatic breast cancer and the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

Metastatic Pancreatic Cancer

A multicentre, multinational, randomized, open-label study was conducted in 861 patients to compare nab-paclitaxel /gemcitabine versus gemcitabine monotherapy as first-line treatment in patients with metastatic adenocarcinoma of the pancreas. Patients who received adjuvant chemotherapy were not eligible for enrollment. nab-paclitaxel E was administered to patients (N=431) as an intravenous infusion over 30-40 minutes at a dose of 125 mg/m^2 followed by gemcitabine as an intravenous infusion over 30-40 minutes at a dose of 1000 mg/m^2 given on Days 1, 8 and 15 of each 28-day cycle. In the comparator treatment group, gemcitabine monotherapy was administered to patients (N=430) as 1000 mg/m^2 given weekly for 7 weeks followed by a 1 week rest period in Cycle 1 and in Cycle 2 and onwards was administered on Days 1, 8 and 15 of a 28-day cycle (consistent with the label recommended dose and regimen). Treatment was administered until disease progression or development of an unacceptable toxicity.

Evidence from the pivotal clinical study in metastatic pancreatic cancer suggest that patients 75 years or older who received nab-paclitaxel in combination with gemcitabine had a higher risk of serious adverse reactions and adverse reactions that led to treatment discontinuation. No survival benefit for the combination treatment of nab-paclitaxel and gemcitabine has been demonstrated for patients 75 years and older, however, clinical studies did not include sufficient number of patients with metastatic pancreatic cancer in this age group to determine whether they respond differently from younger patients.

3.5.4 *Adverse Reaction Overview in Metastatic Pancreatic Cancer*

In the phase III study of metastatic pancreatic cancer, the most common treatment emergent adverse events (≥ 20%) in patients receiving nab-paclitaxel in combination with gemcitabine were: fatigue (59%), nausea (54%), peripheral neuropathy SMQ (54%), alopecia (50%), peripheral edema (46%), diarrhea (44%), anemia (42%), neutropenia (42%), pyrexia (41%), vomiting (36%), decreased appetite (36%), constipation (30%), thrombocytopenia (30%), rash (28%), abdominal pain (23%), and dehydration (21%). Approximately 50% of patients receiving nab-paclitaxel and gemcitabine experienced serious adverse events, including pyrexia, vomiting dehydration and pneumonia. Adverse reactions resulting in death within 30 days of the last dose of study drug were reported for 4% of patients in the nab-paclitaxel and gemcitabine group and for 4% of patients in the gemcitabine group.

3.5.5 *Pharmaceutical Data*

Supplied:
Commercial supply of nab-paclitaxel will be used in this study. See label/package insert for additional information.

Route of Administration:
Nab-paclitaxel is administered intravenously.

4.0 STUDY POPULATION

Patients with metastatic ductal adenocarcinoma of the pancreas who are suitable candidates for first-line standard chemotherapy.

Patients may have received prior adjuvant chemotherapy if last dose was given more than 6 months prior to recurrence. Patients may not have received adjuvant chemoradiotherapy.

Prior treatment for borderline resectable or locally advanced disease is not permitted.

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

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

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

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

4.1.1 Patients must have histologically or cytologically confirmed pancreatic ductal adenocarcinoma which is metastatic.

4.1.2 Must have presence of measurable or evaluable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

4.1.3 Patients must be considered suitable candidates for, and able to receive, first line chemotherapy for metastatic disease with gemcitabine and nab-paclitaxel.

4.1.4 Patient must consent to provision of, and investigator(s) must confirm access to and agree to submit within 4 weeks of randomization to the CCTG Central Tumour Bank, a representative formalin fixed paraffin block of tumour tissue of adequate amount and quality in order that the specific correlative marker assays proscribed in the protocol may be conducted. Cytospin and brushings are not considered to be sufficient. Sites undertaking genomic profiling may contact CCTG to discuss submission of tumour tissue sufficient for patient eligibility.

Where adequate amount and quality of tissue exists but local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to randomization 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. Where tumour tissue is available, failure to submit any tissue samples will result in the patient being considered ineligible. Where no previously resected or biopsied tumour tissue exists or is found to be of inadequate amount or quality, additional biopsy of the primary or metastatic tumour will be required for the patient to be considered eligible for the study. Please refer to the PA.7 correlative tissue manual for details concerning adequacy of amount and quality of tumour tissue.

4.1.5 Patient must consent to provision of samples of blood, serum and plasma in order that the specific correlative marker assays proscribed in Section 12.0 may be conducted.

4.1.6 Patients must be ≥ 18 years of age.

4.1.7 Patients must have an ECOG performance status of 0 or 1 with a life expectancy of at least 12 weeks.

4.1.8 No prior treatment for metastatic disease is permitted. Patients may have received prior adjuvant chemotherapy if the last dose was given more than 6 months prior to recurrence. Patients may not have received adjuvant chemoradiotherapy or adjuvant radiation therapy. Patient may not have received nab-paclitaxel as adjuvant therapy. Prior systemic treatment for borderline resectable or locally advanced disease is not permitted. Patients receiving a single dose of radiation (up to 8 Gy / 800 RAD) with palliative intent for pain control are eligible provided a minimum of 14 days have elapsed between the radiation and the date of randomization.

4.1.9 Adequate normal organ and marrow function as defined below (must be done within 14 days prior to registration).

Hematology	Absolute neutrophils	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
	Hemoglobin	≥ 90 g/L
Biochemistry	Bilirubin	≤ 1.5 x ULN (upper limit of normal)*
	AST and ALT **	≤ 2.5 x ULN
	Serum creatinine *or:* Creatinine clearance***	< 1.25 x ULN ≥ 40 mL/min

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

** < 3 x UNL in presence of liver metastases

*** 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

Males: GFR = 1.23 x (140-age) x weight in kg / serum creatinine in µmol/L

4.1.10 Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease done within 28 days prior to randomization.

4.1.11 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French. The baseline assessment must be completed within required timelines, prior to registration/randomization. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

4.1.12 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrolment in the trial to document their willingness to participate. A similar process must be followed for sites outside of Canada as per their respective cooperative group's procedures.

4.1.13 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. Patients must agree to return to the participating centre for management of any adverse events which may occur through the course of the trial. This implies there must be reasonable geographical limits placed on patients being considered for this trial. Sites are encouraged to contact CCTG (or their respective Cooperative Group for sites outside Canada) for any questions regarding the interpretation of this criterion. Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

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

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

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

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

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

4.2 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 ≥ 5 years. Patients with a history of other malignancies detected at an early stage and whom the investigator believes have been curatively treated and are at a low risk of recurrence MAY be eligible. Contact CCTG to discuss eligibility prior to enrolling.

4.2.2 Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA4, including tremelimumab.

4.2.3 History of primary immunodeficiency, history of organ transplant that requires therapeutic immunosuppression or prior history of severe (grade 3 or 4) immune mediated toxicity from other immune therapy.

4.2.4 Current or prior use of immunosuppressive medication within 28 days before the first planned dose of study therapy, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

4.2.5 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.

NOTE: Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

4.2.6 Patients with active or uncontrolled intercurrent illness including, but not limited to:

- cardiac dysfunction (symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia);
- active peptic ulcer disease or gastritis;
- active bleeding diatheses;
- psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent;
- known history of previous clinical diagnosis of tuberculosis;

- known human immunodeficiency virus infection (positive HIV 1/2 antibodies);
- known active hepatitis B infection (positive HBV surface antigen (HBsAg)). Patients with a past or resolved HBV infection (defined as presence of hepatitis B core antibody (anti-HBc) and absence of HBsAg) are eligible;
- known active hepatitis C infection. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

4.2.7 History of leptomeningeal carcinomatosis.

4.2.8 Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.

4.2.9 Receipt of live attenuated vaccination (examples include, but are not limited to, vaccines for measles, mumps, and rubella, live attenuated influenza vaccine (nasal), chicken pox vaccine, oral polio vaccine, rotavirus vaccine, yellow fever vaccine, BCG vaccine, typhoid vaccine and typhus vaccine) within 30 days prior to randomization.

4.2.10 Pregnant or lactating women.

4.2.11 Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy.

4.2.12 Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol.

4.2.13 History of hypersensitivity to gemcitabine, nab-paclitaxel, durvalumab or tremelimumab or any excipient.

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 (≤14 days prior to randomization)	During Protocol Treatment			After Protocol Treatment[1]	
		Day 1 each cycle, and as clinically indicated	Day 8 each cycle, and as clinically indicated	Day 15 each cycle	4 weeks after end of last cycle date	3 month follow-up
History and Physical Exam[2]						
Including: height (baseline only), weight, BSA, ECOG performance status	X	X			X	X until objective progression
Vital Signs (blood pressure, heart rate, temperature)	X	X[3]				
Concomitant Medications	X	X			X	
Clinical tumour measurements (if applicable)[4]	X	Every 8 weeks from start of treatment until objective progression.				
Hematology[2]						
CBC, differential (including lymphocytes), platelets,	X	X	X	X	X	X[5]
Coagulation[2]						
PTT, PT/INR	X	X	X cycle 1 only and as clinically indicated	as clinically indicated	X	X[5]
Biochemistry[2]						
serum creatinine, chloride, sodium, potassium, calcium, magnesium, bilirubin, ALP, AST, and/or ALT[17], LDH, Albumin, TSH[6], Amylase, Lipase[17]	X	X[7]	X[8] cycle 1 only and as clinically indicated	as clinically indicated	X	X[5]
Creatinine Clearance (calculated)	X	as clinically indicated				
Glucose	X	as clinically indicated				
Urea or BUN	X	as clinically indicated				
Radiology[9]						
Chest/abdomen/pelvis CT scan	X ≤ 28 days	Every 8 weeks from start of treatment [4] until objective progression				
Other scans as necessary to document all measurable and non-measurable disease	X ≤ 28 days					
Other Investigations						
Pregnancy Test[10]	X					
Dipstick Urinalysis (including protein, specific gravity, glucose and blood)	X	as clinically indicated				
ECG	X					

table continues on next page ...

Required Investigations	Pre-study (≤14 days prior to randomization)	During Protocol Treatment			After Protocol Treatment[1]	
		Day 1 each cycle, and as clinically indicated	Day 8 each cycle, and as clinically indicated	Day 15 each cycle	4 weeks after end of last cycle date	3 month follow-up
Correlative Studies						
Archival Tissue Sample[11]	Availability of sufficient tissue must be confirmed prior to randomization					
Tumour Biopsy (*optional at participating sites for consenting patients only*)		At 8 weeks on treatment				
Whole blood, plasma and serum	After randomization but before first dose of study treatment	At 8 weeks and at the time of progression[12], if not already done See Section 12.0 and PA.7 Laboratory Manual for details.				
Adverse Events						
Adverse Event Assessment[13]	≤ 14 days (To document residual adverse events form previous therapy and baseline symptoms)	X[7] To be evaluated continuously for adverse events			X	X[14]
Quality of Life						
EORTC QLQ C30[15]	≤ 14 days	At 4, 8, 12, 16 and 24 weeks after randomization, then every 12 weeks thereafter			X	X[16]

footnotes on next page ...

1. All patients will be seen at 4 weeks after the end of the last cycle date. Thereafter, continued follow-up is not required for patients who go off protocol treatment with unequivocal progressive disease, except to document ongoing toxicities (until resolved to < grade 2) and late toxicities (including second malignancies) and for survival status. For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 8 weeks until relapse (see Appendix I for investigations to be performed). Death Report will be required for all patients. Due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).
2. Timing of Assessments: Pre-treatment blood draws and physical exams may be done one working day prior to treatment if and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). 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 III 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. Note: Labs do not need to be repeated D1C1. In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours prior to the day specified in the protocol.
3. Patients will be monitored before, during infusion and after the infusion of tremelimumab and durvalumab with assessment of vital signs to be collected ≤ 30 minutes prior to start of infusion then every 30 ±5 minutes during infusion and observation periods. A 1-hour observation period is recommended after the tremelimumab, during which time durvalumab may be administered (see 7.2.4). A second 1-hour observation period is recommended after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle of tremelimumab+durvalumab therapy, subsequent infusion observation periods can be at the investigator's discretion but are recommended to be of 30 minutes (i.e. 30 minutes after tremelimumab infusion, during the durvalumab infusion and for 30 minutes after the durvalumab infusion. For patients who receive only durvalumab, the recommended observation period is 30 minutes after the infusion. The standard chemotherapy (nab-paclitaxel followed by gemcitabine) may be administered during the observation period according to local practice.
4. Lesion status assessment must be consistently performed every eight weeks counting from the first day of protocol treatment (i.e. day 1, cycle 1). Sites should adhere to this 8 week calendar based schedule regardless of any delays in treatment cycles. If a clinical lesion status assessment is done off schedule (e.g. early at 4 weeks), future protocol-required clinical lesion status assessments should still be performed based on the original schedule, i.e. every eight weeks counting from the first day of protocol treatment (not 6 weeks from the date of the off schedule assessment). For patients on Arm 2 (durvalumab + tremelimumab containing arm) who remains on protocol therapy after the RECIST 1.1 criteria for progression has been met must have imaging to for disease assessment done 4-8 weeks after PD by RECIST 1.1. Imaging is desirable 4- 8 weeks after progression is first documented by RECIST 1.1 for patients who receive further treatment. No additional scans are required if patients commence second line treatment.
5. Hematology, Coagulation and Biochemistry investigations to be done after objective progression ONLY if there are ongoing hematologic AEs that are related to protocol treatment.
6. If abnormal, T3 and T4 must be measured.
7. See Section 7 and Appendix III for additional monitoring of patients with toxicity.
8. Amylase and lipase are required on Day 1 of each cycle only.
9. To ensure comparability, baseline scans and subsequent scans to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
10. For women of childbearing potential only. May be urine or serum. Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule-out pregnancy.
11. Archival tissue, blood, plasma and serum samples mandatory. The tissue sample should be submitted within 4 weeks of registration/randomization. See Section 12.0 for details.
12. Whole blood, plasma and serum should be obtained as close to the time of objective progression as possible and should be done within 28 days (e.g. at the next clinic visit). Blood for correlatives done within 28 days PRIOR to date of progression does not need to be repeated. If patient has documented PD prior to 8 week assessment, addition bloodwork at 8 weeks is not required. See Correlative manual
13. Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) (see Appendix V).
14. Only follow adverse events felt to be related to study therapy until resolved to ≤ grade 2.
15. To be completed by patient in clinic
16. QoL to be completed until PD, or the initiation of another anti-cancer treatment, or deterioration to ECOG PS 4 or hospitalization for end of life care; whichever comes first.
17 It is preferable that both i) amylase and lipase and ii) AST and ALT parameters are assessed. For sites where only 1 of these parameters is routinely measured then either i) lipase or amylase or ii) AST or ALT is acceptable.

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 plus an annual short follow up form. Data submission for ineligible participants who have received at least one dose of protocol therapy (experimental or standard treatment, irrespective of allocation) should be followed according to the protocol to allow for treatment and adverse event assessment.

NOTE: The dates of objective progression and death must be reported for ineligible patients.

6.0 ENTRY/RANDOMIZATION PROCEDURES

6.1 Entry Procedures

All registration/randomizations will be done through the CCTG web-based, password-protected Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the PA.7 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients please contact the help desk (link in EDC) or the PA.7 Study Coordinator.

All eligible patients enrolled on the study by each participating 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 PA.7)
- 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 5.0, including dates of essential tests and actual laboratory values
- BSA, height and weight
- stratification factors

6.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight. This principle applies to individuals whose calculated surface area is 2.2 m^2 or less. In those rare cases where a patient's surface area is greater than 2.2, the actual surface area or 2.2 may be used CCTG BSA calculations are based on the Mosteller formula. Note: Where local standard of care is to utilize 2.0 m^2 as maximum, this is also permitted.

6.3 Stratification

Subjects will be stratified by:

- ECOG performance status (0 vs 1)
- prior adjuvant therapy (yes vs no)

6.4 Registration / Randomization

Registration / Randomization will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the patient 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 treating physician to satisfy himself or herself that the patient is indeed eligible before requesting registration/randomization.

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

7.0 TREATMENT PLAN

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

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

One cycle will be defined as 28 days.

All patients will receive standard chemotherapy with gemcitabine and nab-paclitaxel and the chemotherapy treatment plan is the same regardless of the arm of the trial they are allocated to.

7.1 Treatment Plan Overview

7.1.1 *Safety Run-In*

Prior to the randomized component of this study, ten patients will be enrolled into Arm 2 at the doses outlined in the table below. Once the tenth patient has been registered the 10 patients will be observed for safety concerns until the end of the first cycle. If no safety concerns (i.e. unexpected severe toxicity) are identified the randomized component of the trial will be initiated.

When durvalumab is given with tremelimumab, tremelimumab will be administered first. Durvalumab infusion will start immediately after the tremelimumab infusion (during the post-tremelimumab observation period) and standard chemotherapy will start after the end of the durvalumab infusion.

Safety Run-In	Agent(s)	Dose	Route	Duration	Schedule
Arm 2	Gemcitabine	1000 mg/m^2	IV	until unequivocal progression or unacceptable toxicity	D1, D8, D15 Q28 days
	Nab-Paclitaxel	125 mg/m^2	IV		
	Durvalumab	1500 mg	IV		D1 only Q28 days
	Tremelimumab	75 mg	IV		D1 cycles 1, 2, 3 and 4 only

See Sections 7.2.2 for patient monitoring and dose adjustments.

7.1.2 *Phase II –Randomized to Standard Chemotherapy +/- Durvalumab AND Tremelimumab*

Following the analysis of safety run-in component of this study, patients will be randomized to receive either standard chemotherapy (ARM 1) or standard chemotherapy plus durvalumab and tremelimumab (ARM 2) at the doses outlined in the table below. Randomization will be 2:1 in favour of the investigational arm (ARM 2).

Arm	Agent(s)	Dose	Route	Duration	Schedule
1	Gemcitabine	1000 mg/m^2	IV	until unequivocal progression or unacceptable toxicity	D1, D8, D15 Q28 days
	Nab-Paclitaxel	125 mg/m^2	IV		
2	Gemcitabine	1000 mg/m^2	IV	until unequivocal progression or unacceptable toxicity	D1, D8, D15 Q28 days
	Nab-Paclitaxel	125 mg/m^2	IV		
	Durvalumab*	1500 mg	IV		D1 only Q28 days
	Tremelimumab*	75 mg	IV		D1 cycles 1, 2, 3 and 4 only
* When durvalumab is given with tremelimumab, tremelimumab will be administered first. Durvalumab infusion will start immediately after the tremelimumab infusion (during the post-tremelimumab observation period) and standard chemotherapy will start 15 minutes after the end of the durvalumab infusion.					

7.2 Patient Treatment and Monitoring by Arm

Consult the Pharmacy Information Manual for complete details

7.2.1 *Patient Treatment and Monitoring for ARM 1 - Standard Chemotherapy (Gemcitabine +Nab-Paclitaxel)*

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

Premedication is not expected to be required, e.g. for nausea or prophylaxis for hypersensitivity. Management of symptoms should take place as necessary. Details of any premedication or concomitant medication given to manage or prevent adverse events should be recorded on the electronic case report form (eCRF).

Order of Infusion:
The nab-paclitaxel should be administered prior to the gemcitabine.

The recommended dose of Nab-paclitaxel is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. The recommended dose of gemcitabine is 1000 mg/m^2 as an intravenous infusion over 30-40 minutes beginning immediately after the completion of Nab-paclitaxel administration on Days 1, 8 and 15 of each 28-day cycle.

Patient Monitoring:
Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of Nab-paclitaxel to 30 minutes, or as directed per the study protocol, reduces the likelihood of infusion-related reactions.

7.2.2 *Patient Treatment and Monitoring for ARM 2 - Standard Chemotherapy (Gemcitabine +Nab-Paclitaxel) + Tremelimumab + Durvalumab*

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

Premedication is not expected to be required, e.g. for nausea or prophylaxis for hypersensitivity. Management of symptoms related to the durvalumab and/or tremelimumab should take place as necessary (see Appendix III). See Sections 7.3.2 and 7.6 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).

Order of Infusion:
When durvalumab is given with tremelimumab, tremelimumab will be administered first. Durvalumab infusion may start immediately after the tremelimumab infusion (during the post-tremelimumab observation period) and standard chemotherapy will start 15 minutes after the end of the durvalumab infusion. The nab-paclitaxel should be administered prior to the gemcitabine.

Patient Monitoring:
Patients will be monitored before, during infusion and after the infusion of tremelimumab and durvalumab or durvalumab alone with assessment of vital signs as specified in Section 5.0. A 1-hour observation period is recommended after the first durvalumab or tremelimumab infusion period which may run concurrently. After the first cycle, subsequent observation periods can be at the discretion of the investigator (30 minutes is suggested).

Patients should be monitored for signs and symptoms of immune related AEs (see Appendix III). In the absence of an alternate etiology (e.g. infection or relapse), signs or symptoms of events with a potential inflammatory or immune-mediate mechanism should be considered to be immune-related. Guidelines for management of infusion-related reaction are summarized below and in Appendix III.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of Nab-paclitaxel to 30 minutes, or as directed per the study protocol, reduces the likelihood of infusion-related reactions.

Management of Infusion Reactions:

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

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

Drug Administration and Patient Monitoring/Vitals for ARM 2:

<table>
<tr><th>Drug administration</th><th>Infusion duration</th><th colspan="2">Vital signs and Monitoring*</th></tr>
<tr><td>Tremelimumab</td><td>60 min</td><td rowspan="2">First infusion: Vital signs ≤ 30 minutes prior to start of infusion then every 30 ±5 minutes during infusion and observation periods
Subsequent infusions: At Investigator's discretion</td><td rowspan="2">First infusion: 60 min observation period after administration of 1st cycle of durvalumab/tremelimumab
Subsequent infusions: At Investigator's discretion (30 min recommended)</td></tr>
<tr><td>Durvalumab</td><td>60 min</td></tr>
<tr><td>Nab-Paclitaxel</td><td>30-40 min**</td><td colspan="2" rowspan="2">Infusion may begin 15 minutes after end of durvalumab and may continue through the observation period for the durvalumab.</td></tr>
<tr><td>Gemcitabine</td><td>30-40 min**</td></tr>
<tr><td colspan="4">* Guidelines for management of infusion-related reaction are summarized below and in Appendix III.
** Duration of infusion should be according to local protocol.</td></tr>
</table>

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

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

7.3 Adverse Event Management and Dose Modification and Adjustments

7.3.1 *Overview (BOTH Arms)*

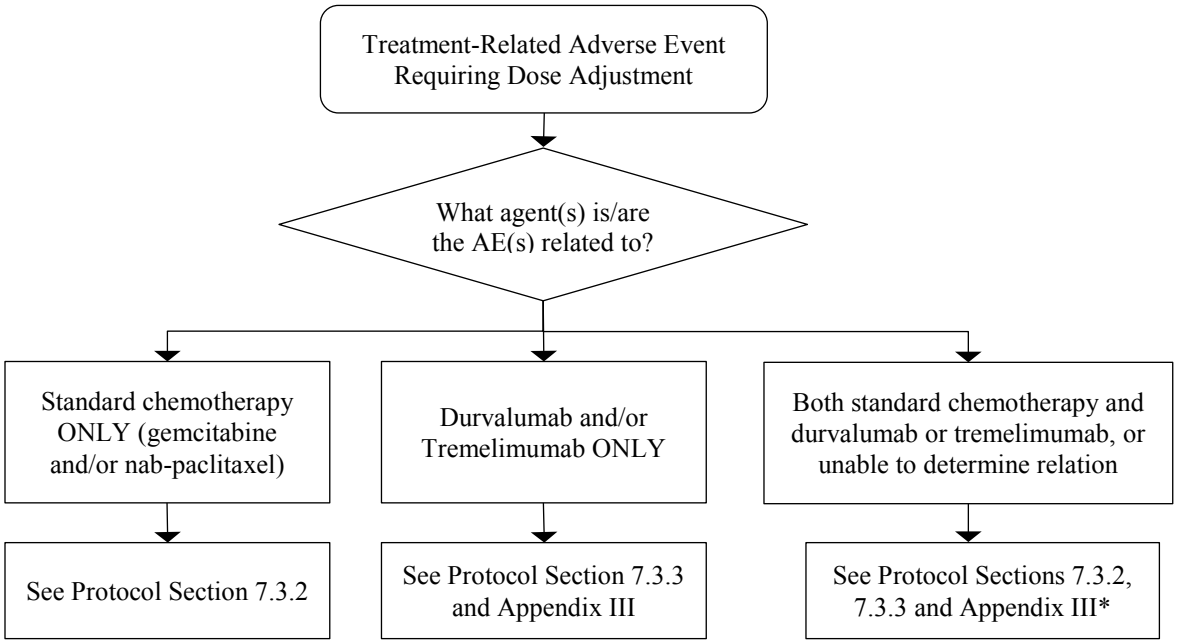
Doses will be reduced for adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Toxicity Criteria Version 4.0 (see Appendix V). The guidelines which follow outline dose adjustments for several of the potential adverse events related to gemcitabine and nab-paclitaxel and durvalumab + tremelimumab as referenced in the sections below. If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

The maximum delay in the start of the next scheduled cycle should not normally be longer than 21 days. Day 1 of the next planned cycle may be delayed up to 21 days not including any Day 8 or Day 15 omitted doses during the preceding cycle. **Day 1 of a cycle should only delayed due to AEs related to the gemcitabine and/or nab-paclitaxel.** If AEs are related to durvalumab and/or tremelimumab the standard chemotherapy should be maintained and the investigational agent omitted for that cycle (see Section 7.3.2 for additional information).

In the situation where a delay in the start of the next scheduled cycles of nab-paclitaxel or gemcitabine dosing of > 21 days has occurred due to management of toxicities considered potentially associated with both chemotherapy and immune therapy study agents, if it is the opinion of the investigator that the patient would benefit from resumption of gemcitabine and nab-paclitaxel, the CCTG should be contacted for prior approval.

The overarching principle of adverse event management is that dose modifications or adjustments should be made for those study agents considered to be associated with the corresponding adverse events as illustrated in the following diagram:

Flowchart for Dose Modifications



* *If there are conflicting recommendations, use the recommended dose adjustment that reduces the does to the lowest level.*

The recommended dose of Nab-paclitaxel is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. The recommended dose of gemcitabine is 1000 mg/m^2 as an intravenous infusion over 30-40 minutes beginning immediately after the completion of Nab-paclitaxel administration on Days 1, 8 and 15 of each 28-day cycle.

7.3.2 *Dose Modifications for Gemcitabine and Nab-Paclitaxel (Standard Treatment – BOTH Arms)*

Dose Level Reductions for Gemcitabine and Nab-Paclitaxel

Dose Level	Nab-Paclitaxel Dose (mg/m^2)	Gemcitabine Dose (mg/m^2)
Full dose	125	1000
1st dose level reduction	100	800
2nd dose level reduction	75	600
If additional dose reduction required	Discontinue treatment	Discontinue treatment

Rules for Gemcitabine or Nab-Paclitaxel Dose Omissions and Modified Schedules

One cycle is considered to be 28 days. Day 1 of a cycle is defined as the date nab-paclitaxel and gemcitabine are given. Day 1 of a cycle should only delayed due to AEs related to the gemcitabine and/or nab-paclitaxel. **If AEs are related to durvalumab and tremelimumab the standard chemotherapy should be maintained and the investigational agent omitted for that cycle** (see Section 7.3.2 for additional information).

When a dose reduction is required for either gemcitabine or nab-paclitaxel, no dose reescalation will be permitted for the duration of study treatment (with the exception of Day 15, where re-escalation with granulocyte-colony stimulating factor (G-CSF) support is permitted, after a previous dose reduction on Day 8 of the same cycle).

Day 1 dose delayed:
If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e. 1-2-3-Rest, X-1-2-3-Rest, etc.). If patient was randomized to the investigational arm, the durvalumab + tremelimumab (cycles 1 through 4) should also be delayed until patient is able to resume the gemcitabine/nab-paclitaxel and start the next cycle.

Day 8 dose is missed:
Cycle continues per protocol, with one dose not given (i.e. 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc.). Day 8 is administered as per cycle calendar if counts and chemistries permit.

Day 15 dose missed:
Cycle continues per protocol, with the dose not given (i.e. 1-2-3-Rest, 1-2-X- Rest, 1-X-X-Rest, etc.) The 28 day cycle should be maintained and the day 15 dose omitted. Investigators should consider the use of G-CSF for patients who are unable to receive Day 15 or have isolated grade 3 neutropenia and received day 15, in order to ensure the next cycle is given on time.

The maximum delay in the start of the next scheduled cycle should not normally be longer than 21 days. Day 1 of the next planned cycle may be delayed up to 21, days not including any Day 8 or Day 15 omitted doses during the preceding cycle.

In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up. Omitted doses are not considered to be treatment delays.

***Arm 1 (standard chemotherapy): Specific Information for Dose Modifications and Adjustments to Gemcitabine and/or Nab-paclitaxel**:*

Patients enrolled to ARM 1 (standard treatment with gemcitabine and nab-paclitaxel) experiencing study drug-related toxicities that require a delay in the start of the next scheduled cycle of treatment with nab-paclitaxel or gemcitabine dosing for > 21 days for unresolved adverse events related to either nab-paclitaxel or gemcitabine (except for peripheral neuropathy) should normally be discontinued from further treatment in this study. In the situation where it is the opinion of the investigator that the patient would benefit from resumption of study therapy beyond this interval, the CCTG should be contacted for prior approval.

Arm 2 (standard chemotherapy with addition of durvalumab + tremelimumab): Specific Information for Dose Modifications and Adjustments to Gemcitabine and/or Nab-paclitaxel:

Important: For patients randomized the investigational arms (ARM 2), if Day 1 of a cycle is delayed due to AEs related to the gemcitabine and/or nab-paclitaxel, the infusion of durvalumab +/- tremelimumab should also be delayed until the Day 1 treatment may be given. If the patient permanently discontinues treatment with gemcitabine and/or nab-paclitaxel he/she may continue to receive treatment with durvalumab +/- tremelimumab.

If the AEs requiring treatment modifications are only related to durvalumab and/or tremelimumab (see Section 7.3.2), the administration of the gemcitabine and nab-paclitaxel should not be delayed if patient meets the requirements for their administration.

For patients enrolled to ARM 2 experiencing gemcitabine or nab-paclitaxel related toxicities that require a delay in the start of the next scheduled cycle (Day 1) with nab-paclitaxel or gemcitabine dosing for > 21 days for unresolved adverse events (except for peripheral neuropathy), consideration should be given to discontinuation of further gemcitabine and nab-paclitaxel therapy.

Patients on Arm 2 are unable to tolerate gemcitabine or nab-paclitaxel therapy may continue to receive immune therapy study agents.

In the situation where a delay in the start of the next scheduled cycle of nab-paclitaxel or gemcitabine dosing of > 21 days has occurred due to management of toxicities considered potentially associated with both chemotherapy and immune therapy study agents, if it is the opinion of the investigator that the patient would benefit from resumption of gemcitabine and nab-paclitaxel, the CCTG should be contacted for prior approval.

Management of Gemcitabine and Nab-Paclitaxel Related Toxicities

The major toxic effects of gemcitabine and nab-paclitaxel which limit dose are hematologic (neutropenia with or without fever, and thrombocytopenia), peripheral neuropathy, gastrointestinal toxicity (mucositis and diarrhea) and infusion site reactions. 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.

Hematologic Adverse Events at the Start of a Cycle or Within a Cycle for Gemcitabine and Nab-paclitaxel

Cycle Day	Absolute Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Nab-paclitaxel and Gemcitabine dose
Day 1	≥ 1.5	and	> 100	Treat on time at current dose levels
	< 1.5	or	< 100	Delay doses until recovery
Day 8	≥ 1.0	and	≥ 75	Treat on time at current dose levels
	≥ 0.5 but < 1.0	or	≥ 50 but < 75	Treat on time, but reduce doses 1 dose level
	< 0.5	or	< 50	Withhold doses
Day 15: *IF* Day 8 doses were given without modification:				
Day 15	≥ 1.0	and	≥ 75	Treat on time at current dose levels
	≥ 0.5 but < 1.0	or	≥ 50 but < 75	Treat on time at current dose levels and follow with WBC Growth factors[1,2]
	< 0.5	or	< 50	Withhold doses
Day 15: *IF* Day 8 doses were reduced:				
	≥ 1.0	and	≥ 75	Treat on time, but return to Day 1 dose level and follow with WBC Growth factors[1,2]
Day 15	≥ 0.5 but < 1.0	or	≥ 50 but < 75	Treat on time with Day 8 dose level and follow with WBC Growth factors[1,2]
	< 0.5	or	< 50	Withhold doses
Day 15: *IF* Day 8 doses were withheld:				
Day 15	≥ 1.0	and	≥ 75	Treat on time, but return to Day 1 dose level and follow with WBC Growth factors[1,2]
	≥ 0.5 but < 1.0	or	≥ 50 but < 75	Treat on time, but reduce 1 dose level and follow with WBC Growth Factors [1,2]
	< 0.5	or	< 50	Withhold doses

[1] G-CSF optional if descent only affected platelets
[2] If G-CSF is not available, a reduction in dose levels is recommended.

Non-hematologic Adverse Events for Gemcitabine and Nab-paclitaxel

Adverse Drug Reaction	Grade	Nab-paclitaxel Dose	Gemcitabine dose
Febrile Neutropenia	Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1.5; resume at reduced dose levels	
Peripheral Neuropathy	Grade 3 or 4	Withhold dose until improves to ≤ Grade 1; resume at reduced dose level	Treat with same dose
Cutaneous Toxicity	Grade 2 or 3	Treat on time, but reduce doses 1 level; discontinue treatment if adverse event persists	
Gastrointestinal Toxicity: mucositis or diarrhea	Grade 3	Withhold doses until improves to ≤ Grade 1; resume at reduced dose levels	

Abnormal Hepatic Function

Gemcitabine and nab-Paclitaxel should only be administered if hepatic function is within the parameters established in the eligibility criteria, specifically bilirubin ≤ 1.5 x upper limit of normal (ULN) and AST and ALT ≤ 2.5 ULN (<3 x ULN in the presence of liver metastases). Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications, or in the case of patients enrolled to the investigational arm (Arm 2), from durvalumab +/- tremelimumab.

Pulmonary Embolism

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

Interstitial Pneumonitis

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e. episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required).

Other (Non-hematologic) Adverse Events considered related to Gemcitabine or Nab-paclitaxel

Dose Modifications **for Day 1 of Each Cycle** (Non-Hematologic Toxicity)

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	Nab-paclitaxel and Gemcitabine Dose (this cycle)
Grade 0, 1 or 2 toxicity	Same as Day 1 of previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine and nab-paclitaxel should both be reduced to next lower dose level)
Grade 3 toxicity[1]	Decrease gemcitabine and nab-paclitaxel to next lower dose level[1]
Grade 4 toxicity[1,2]	Off protocol treatment[2]

1 If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced.

2 Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or a symptomatic, will be exempt from this requirement.

7.3.3 *Dose Modifications for Durvalumab with Tremelimumab (Arm 2)*

The major toxic effects of durvalumab or tremelimumab which are anticipated to limit dosing are hypersensitivity/ infusion related reactions and possible class related immune related AEs, based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation. These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include immune related AEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy.

Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include diarrhea/colitis, and intestinal perforation, pneumonitis/ILD, ALT/AST increases/hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicities (e.g. Guillain-Barré syndrome, and myasthenia gravis), endocrinopathies (i.e. hypophysitis, hypopituitarism, adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus), rash/dermatitis, nephritis/blood creatinine increases, pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase), myocarditis, and myocitis/polymyositis. Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events. 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.

Patients should be monitored for signs and symptoms of immune related AEs. In the absence of an alternate etiology (e.g. infection or relapse), signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune- related.

Adverse events that are suspect to be immune mediated AND that require intervention with high doses of steroids are considered to be medically important events that require intervention to prevent a fatal, life-threatening or hospitalization event. They should be reported as expedited SAEs. See Section 9.1.2 for additional information.

Guidelines for durvalumab and/or tremelimumab dose modification and toxicity management of immune related and non-immune related events are described in detail in Appendix III.

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

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 reductions are not permitted to the durvalumab and/or tremelimumab. Dose adjustments (slowing/interruption of infusion rate, omission of a dose, or permanent discontinuation) will be made for hematologic and other adverse events that are related to only to durvalumab or tremelimumab**.**

Dose delays are not permitted for AEs related ONLY to the durvalumab and/or tremelimumab.

Patients on Arms 2 who are unable to tolerate durvalumab and/or tremelimumab therapy may continue to receive standard chemotherapy on study.

If a patient has received high dose steroids for management of AEs related to durvalumab +/- tremelimumab, treatment with durvalumab +/- tremelimumab should only be resumed at the next scheduled dose after the event has stabilized to grade ≤ grade 1 and 5-7 days has passed since the completion of the steroid taper. The treatment schedule of the standard chemotherapy (gemcitabine and nab-paclitaxel) should remain unchanged provided the patient meets the requirement for treatment outlined in Section 7.3.1. In other words, the start of a cycle should NOT be delayed due to AEs related only to durvalumab and/or tremelimumab, nor should the start of a cycle be delayed to allow for completion of steroid tapers and wash out periods.

In the situation where a delay in the start of the next scheduled cycles of nab-paclitaxel or gemcitabine dosing of > 21 days has occurred due to management of toxicities considered potentially associated with both chemotherapy and immune therapy study agents, if it is the opinion of the investigator that the patient would benefit from resumption of gemcitabine and nab-paclitaxel, the CCTG should be contacted for prior approval.

The next cycle should not be given until the laboratory criteria in Section 7.3.1 are met and resolution of all drug related toxicity to < grade 2. Discuss with CCTG if asymptomatic/not felt to be clinically significant.

Important: If the infusion cannot be administered, it should be omitted until the next planned infusion. The gemcitabine and nab-paclitaxel schedule should NOT be adjusted if AEs are related only to durvalumab or tremelimumab. Explicitly, start of the next cycle should not be delayed for adverse events related to either durvalumab or tremelimumab, rather Day 1 treatment with the standard chemotherapy (gemcitabine and nab-paclitaxel) should be given on schedule if possible and treatment with durvalumab or tremelimumab omitted until related adverse events have resolved to permit resumption of durvalumab or tremelimumab therapy with subsequent cycles.

For patients enrolled to ARM 2 (addition of durvalumab and tremelimumab), where a dose of tremelimumab is omitted from one or more of the first four cycles of therapy as planned, then the investigator may exercise discretion in adding tremelimumab to subsequent cycles beyond the first 4 with a maximum of 4 doses of tremelimumab administered.

If durvalumab or tremelimumab are omitted for ≥ 2 consecutive cycles due to unresolved adverse events related to durvalumab or tremelimumab, consideration should be given to discontinuing further therapy with durvalumab and/or tremelimumab. However, if it is the investigator's assessment that the patient would benefit from the resumption of durvalumab or tremelimumab therapy, then CCTG should be contacted for prior approval.

Important: For patients randomized to the investigational arms (Arm 2), if Day 1 of a cycle is delayed due to AEs related to the gemcitabine or nab-paclitaxel, the infusion of durvalumab +/- tremelimumab should also be delayed until the Day 1 treatment may be given. If the patient permanently discontinues treatment with gemcitabine and/or nab-paclitaxel he/she may continue to receive treatment with durvalumab +/- tremelimumab.

For patients enrolled to ARM 2 (addition of durvalumab and tremelimumab) experiencing gemcitabine or nab-paclitaxel related toxicities that require a delay in the start of the next scheduled cycles of nab-paclitaxel or gemcitabine dosing for > 21 days for unresolved adverse events (except for peripheral neuropathy), consideration should be given to discontinuation of further gemcitabine and nab-paclitaxel therapy. Patients that are unable to tolerate gemcitabine or nab-paclitaxel therapy may continue to receive immune therapy study agents.

In the situation where a delay in the start of the next scheduled cycle of nab-paclitaxel or gemcitabine dosing of > 21 days has occurred due to management of toxicities considered potentially associated with both chemotherapy and immune therapy study agents, if it is the opinion of the investigator that the patient would benefit from resumption of gemcitabine and nab-paclitaxel, the CCTG should be contacted for prior approval.

Management of Toxicity for Durvalumab +/- Tremelimumab:

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

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

In addition to the dose adjustments shown in Appendix III, the following are recommended:

- Patient evaluation to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
- Symptomatic and topical therapy should be considered for low-grade events.
- For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone PO 1-2 mg/kg/day or IV equivalent.
- If symptoms recur or worsen during corticosteroid tapering (> 4 weeks of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4 mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate.
- More potent immunosuppressive therapy (refer to individual sections of the immune related adverse event for specific type of immunosuppressive agents) 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.

7.4 Duration of Therapy

Protocol treatment will continue until confirmed disease progression as defined in Section 8 or intolerable toxicity. However, a maximum of 4 doses of tremelimumab may be given to patient randomized to the dual immunotherapy arms (Arm 2).

If, in the opinion of the Investigator, a patient is deriving clinical benefit from study therapy despite the documentation of objective disease progression per RECIST 1.1 criteria, then provided the patient does not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient, the patient may remain on study therapy pending their next disease assessment. However, appropriate imaging studies must be repeated within 4-8 weeks to re-assess treatment response. A patient with objective disease progression confirmed on subsequent assessment by either RECIST 1.1 criteria or iRECIST criteria as appropriate, should be discontinued from the study. Patients should also be discontinued from the study if objective disease progression occurs in a target lesion that has previously shown a confirmed response.

For a complete list of general criteria for stopping study treatment, please see Section 10.0.

7.5 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).

7.6 Concomitant Therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study are to be recorded in the eCRF.

7.6.1 *Permitted*

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "not permitted" below. In addition, the following medications or treatments are permitted during the study:

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

7.6.2 *Not Permitted*

- Cytokines
- Other anti-cancer treatment
- Other investigational therapy
- Concurrent radiation treatment; Note: local radiation treatment of isolated lesions for palliative intent is acceptable. Protocol therapy should be held prior to and during the radiation (Consult CCTG in these cases).
- Corticosteroids IV or PO (except for the treatment of ≥ grade 3 infusion reaction and nausea prophylaxis for chemotherapy). Note: Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed, as are oral dose of steroids equivalent to 10 mg or less of prednisone.

- Other immunosuppressive medications including methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs is acceptable.
- Live attenuated vaccines (examples include, but are not limited to, vaccines for measles, mumps, and rubella, live attenuated influenza vaccine (nasal), chicken pox vaccine, oral polio vaccine, rotavirus vaccine, yellow fever vaccine, BCG vaccine, typhoid vaccine and typhus vaccine) within 30 days of durvalumab and tremelimumab dosing (i.e. 30 days prior to the first dose, during treatment with durvalumab and tremelimumab and for 30 days post discontinuation of durvalumab and tremelimumab). Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

7.6.3 *Steroid Tapering Guidelines*

IMPORTANT: Adverse events that are suspected to be immune mediated AND that require intervention with high doses of steroids as described in Appendix III are considered to be medically important events that require intervention to prevent a fatal, life-threatening or hospitalization event should be reported as expedited events using the SAEs reporting system (see Section 9).

If the patient experiences immune-mediated toxicity, they may receive moderate to high-dose steroid therapy for multiple weeks. During the time frame the patient is receiving the steroid, treatment with durvalumab +/- tremelimumab should be omitted and treatment with standard chemotherapy should continue if patient is well enough, in the investigator's opinion, to receive the gemcitabine and nab- paclitaxel. Per guidelines contained in Appendix III, durvalumab +/- tremelimumab may resume once event stabilizes to Grade ≤1 after completion of steroid taper.

Length of steroid tapering is usually dictated by the severity of the immune mediated adverse event and regular monitoring during tapering is strongly recommended, as there is an increased risk of recurrence of the immune mediated adverse event. Local protocols for tapering schedules maybe be followed.

More potent immunosuppressive therapy (refer to individual sections of the immune related adverse event for specific type of immunosuppressive agents in Appendix III) should be considered for events not responding to systemic steroids.

If symptoms recur or worsen during corticosteroid tapering, increase the corticosteroid dose until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate

Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/study regimen should normally require the patient to discontinue durvalumab and/or tremelimumab.

If a patient has received high dose steroids for management of AEs related to durvalumab +/- tremelimumab, treatment with durvalumab +/- tremelimumab should only be resumed at the next scheduled dose after the event has stabilized to grade ≤ grade 1 and 5-7 days has passed since the completion of the steroid taper. The treatment schedule of the standard chemotherapy (gemcitabine and nab-paclitaxel) should remain unchanged provided the patient meets the requirement for treatment outlined in Section 7.3.1. In other words, the start of a cycle should NOT be delayed due to AEs related only to durvalumab and/or tremelimumab, nor should the start of a cycle be delayed to allow for completion of steroid tapers and wash out periods.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Adverse Events*

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

8.1.2 *Evaluable for Response*

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

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

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

8.1.3 *Evaluable for Quality of Life Assessment*

All patients who have completed the quality of life questionnaire are evaluable for quality of life.

8.2 RECIST 1.1 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as the Immune-Related modified Response Criteria (iRECIST)).

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 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

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 *RECIST 1.1 Response*

8.2.5.1 *RECIST 1.1 - Patients With Measurable Disease*

RECIST 1.1 response will be classified as outlined below:

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

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.

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

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

Table 1: Integration of Target, non-Target and New Lesions into Response Assessment *for patients with measurable disease*:

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 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, tumour nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

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

8.2.5.2 *RECIST 1.1 - Patients With Non-Measurable Disease Only*

Patients with only non-measurable (but evaluable) disease, may only have an overall RECIST 1.1 response or SD or PD as follows:

Complete Response (CR): disappearance of non-target lesions. Residual lesions 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.

Stable Disease (SD): steady state of disease. No new lesions and not sufficient progression of non-target lesions to qualify for PD.

Progressive Disease (PD): the appearance of new lesions and/or unequivocal progression of non-target lesions.

Table 2: Integration of Target, non-Target and New Lesions into Response Assessment *for patients with only non-measurable, evaluable, lesions*:

Non-Measurable Lesions*	New Lesions	Overall Response	Best Overall Response for this category also requires
Complete disappearance	No	CR	
Non-PD	No	SD	Documented at least once ≥ 4 weeks from baseline
PD**	No	PD	No prior SD
Any	Yes	PD	

* Note that these lesions should be recorded under the "Non-Target" lesions table on the CRFs.
** Unequivocal progression in non-measurable lesions will be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

8.3 Immune-Related (iRECIST) Response Assessment

Overall response will also be assessed using iRECIST *[Seymour 2017]*. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, 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.

8.3.1 *Confirming Progression*

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

iCPD is confirmed if further 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.

8.3.2 *New Lesions*

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

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case report 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 3: 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 4: iRECIST Best Overall Response (iBOR)

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 randomised 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.

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

8.3.3 *iRECIST - Patients With Non-Measurable Disease Only*

Table 5: Immune-Related RECIST Criteria (iRECIST) *for patients with only non-measurable, evaluable lesions*:

Response	Description of Response	Confirmation by
Complete remission: iCR	Complete disappearance of all non-measurable lesions (and no new lesions). Patient may have had prior iuPD by RECIST 1.1 criteria.	Repeat, consecutive assessment no less than 4 weeks from the date first documented
Stable Disease: iSD	Not meeting criteria for iCR in absence of iPD. Patient may have had prior iuPD by RECIST 1.1 criteria	
Progressive disease: iPD	Unequivocal increase in tumour burden	Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented is required
New measurable lesions (i.e. ≥ 10 mm in long axis)	Measured but not incorporated into overall assessment of target lesions.	
New, non-measurable lesions	Recorded	

8.4 Response Duration (RECIST 1.1 and iRECIST)

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

8.5 Stable Disease Duration

Stable disease duration will be measured from the time of start of 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. 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. 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

9.1.1 *ARM 1 - Standard Treatment (Gemcitabine + Nab-Paclitaxel)*

Arm 1 (Standard Treatment with gemcitabine and nab-paclitaxel) does not contain investigational agents, and adverse events occurring as a result of this commercially available treatment should be reported to CCTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified.

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 9.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the product monograph or package insert.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

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

9.1.2 *ARM 2 (including Safety Run-In) - Investigational Treatment (Gemcitabine + Nab-Paclitaxel + Durvalumab + Tremelimumab)*

- 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 9.3 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

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.

IMPORTANT NOTES:

Adverse events that are suspect to be immune mediated AND that require intervention with high doses of steroids are considered to be medically important events. They should be reported as expedited events using the SAEs reporting system.

If a patient shows an AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN, refer to Appendix III 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.

9.1.3 *Durvalumab + Tremelimumab Adverse Events of Special Interest*

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring An AESI may be serious or non-serious.

AESIs for durvalumab ± tremelimumab include, but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. **These AESIs may require close monitoring in the treatment arms with durvalumab =/- tremelimumab.**

An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the CCTG.

AESIs observed with durvalumab ±tremelimumab include:

- Diarrhea / Colitis, and intestinal perforation;
- Pneumonitis / ILD;
- ALT/AST increases / hepatitis / hepatotoxicity;
- Neuropathy / neuromuscular toxicities (e.g. Guillain-Barré syndrome, and myasthenia gravis);
- Endocrinopathies (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus);
- Rash / Dermatitis;
- Nephritis / Blood creatinine increases;
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase);
- Myocarditis;
- Myocitis/polymyositis;
- Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in Appendix III.

9.1.4 *Events Not to be Treated as SAEs (Both Treatment Arms and Safety Run-in)*

Serious adverse events which are unequivocally related to the underlying malignancy or disease progression do **NOT** require expedited reporting. These include such adverse events as admission for pain control, palliative care or paracentesis of malignant effusions.

- In addition, the following events will **NOT** be recorded as AEs (or SAEs):
  - lack of efficacy /disease progression (will be recorded separately on CRF);
  - laboratory abnormalities for protocol specified tests (these are derived electronically from actual values supplied and need not be reported separately in adverse event tables on CRFs);

- elective hospitalization for medical, radiological or surgical procedures for treatment of disease or to simplify treatment for study procedures (will be recorded separately on CRF);
- hospitalization for palliative care or pain control.

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 PA.7 section of the CCTG website (www.ctg.queensu.ca).

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

Within 10 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:

PA.7 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

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 PA.7 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

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

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.15. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

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

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

9.3.2 *Pregnancy Reporting*

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

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

The investigator is required to report to Canadian Cancer Trials Group (CCTG) any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 6 months after the last dose of study treatment must also be reported.

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

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

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

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

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

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 can not be ruled out).

9.5 CCTG Reporting Responsibility to AstraZeneca

AstraZeneca will be notified of all protocol reportable serious adverse events (as defined in Section 9.1) within one working day of receipt of report at CCTG. CCTG, as sponsor, will determine regulatory re-portability 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 AstraZeneca Reporting Responsibilities

AstraZeneca will report all regulatory reportable serious adverse events from non-CCTG trials (Safety Updates) with durvalumab and tremelimumab to CCTG within the timelines outlined in the contract. CCTG will review these events to determine which meet the criteria (serious, unexpected, drug related) for reporting to PA.7 investigators. AstraZeneca will report these events to Health Canada.

9.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial PA.7 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 PA.7 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 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 and Appendix III.
- 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

Investigators are encouraged to continue therapy, as appropriate in the absence of unacceptable toxicity, until disease progression has been unequivocally documented.

For patients randomized to the gemcitabine + nab-paclitaxel + durvalumab + tremelimumab arm ONLY, study therapy may be continued beyond the first documentation of objective disease progression (i.e. per RECIST 1.1 criteria) on the basis of clinical benefit; continued follow-up assessments per protocol must also be continued until disease progression has been unequivocally confirmed, either through RECIST 1.1 or Immune-Related Response Criteria (iRECIST) (i.e. treatment failure), at which time study therapy should cease.

10.3 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

10.4 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ Grade 2) and late toxicities (including second malignancies) and for survival status. For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 8 weeks until relapse (see Section 5 for investigations to be performed). Final report (Form 6) will be required for ALL patients, due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).

For patients randomized to the gemcitabine + nab-paclitaxel + durvalumab + tremelimumab arm (Arm 2) study therapy may be continued beyond the first documentation of objective disease progression (i.e. per RECIST 1.1 criteria) on the basis of clinical benefit; and the possibility of pseudoprogression. Continued follow-up assessments per protocol must also be continued until disease progression has been unequivocally confirmed, either through RECIST 1.1 or Immune-Related Response Criteria (iRECIST) (i.e. treatment failure), at which time study therapy should cease.

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Radiology Review

There will be no central radiology review for this study.

11.2 Central Pathology Review

There will be no upfront central pathology review for this study, however, per Section 4.1.4 patients must consent to provision of, and investigator(s) must confirm access to and agree to submit within 4 weeks of randomization to the CCTG Central Tumour Bank, a representative formalin fixed paraffin block of tumour tissue of adequate amount and quality in order that the specific correlative marker assays proscribed in the protocol may be conducted. Cytospin and brushings are not considered to be sufficient. Where adequate amount and quality of tissue exists but local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to randomization 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. Where tumour tissue is available, failure to submit any tissue samples will result in the patient being considered ineligible. Where no previously resected or biopsied tumour tissue exists or is found to be of inadequate amount or quality, additional biopsy of the primary or metastatic tumour will be required for the patient to be considered eligible for the study. Please refer to the PA.7 correlative tissue manual for details concerning adequacy of amount and quality of tumour tissue.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual is provided on the PA.7 trial specific website, which will include details regarding sample collection, preparation, handling and shipping.

Tissue samples collected on this trial may be used by researchers now or in the future to better understand the nature of pancreas cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a tumour banking code assigned at the time of sample receipt. Material issued to researchers will be anonymized and identified by tumour banking coded number.

Future use of the banked samples (optional) will undergo a scientific review process of any proposals to use the tissue and any proposals approved will have undergone ethics approval.

Specific samples to be collected and priority assays are as follows:

12.1 Protocol-Mandated Correlative Studies

Tissue Submission (Mandatory)

Archival Tumour Block/Slides:
The submission of a representative block of the diagnostic tumour tissue is an important part of this trial and is mandatory for participation in this trial. Submitted tissue samples will be carefully stored as part of the CCTG Tumour Tissue Data Repository at Queen's University in Kingston, Ontario, and the only assays done will be as part of this study.

All patients must consent to provision of, and investigators must confirm access to and agree to submit, within 4 weeks of randomization to the CCTG Central Tumour Bank, a representative formalin fixed paraffin block of tumour tissue of adequate amount and quality in order that the specific correlative marker assays proscribed in the protocol may be conducted. Cytospin and brushings are not considered to be sufficient.

Tumour tissue may be from a prior primary resection or a sample of metastatic tissue may be submitted, but the preferred tumour sample for the determination of a patient's PD-L1 status is the one taken following the completion of adjuvant therapy (if applicable).

Note: One block of adjacent normal tissue is also requested if available, but is not mandated.

Sites undertaking genomic profiling may contact CCTG to discuss submission of tumour tissue sufficient for patient eligibility.

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

Where adequate amount and quality of tissue exists but local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to randomization 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. Where tumour tissue is available, failure to submit any tissue samples will result in the patient being considered ineligible.

Where no previously resected or biopsied tumour tissue exists or is found to be of inadequate amount or quality, additional biopsy of the primary or metastatic tumour will be required for the patient to be considered eligible for the study.

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

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

Detailed instructions for FFPE sample acquisition, preparation, and shipping are found in the PA.7 Lab Manual.

Planned priority assays on archival tumour tissue include:

a. Immunohistochemistry for PD-L1 and CTLA-4 expression;
b. Immunohistochemistry for tumour infiltrating lymphocytes (CD8+ T cells);
c. Other exploratory analysis by IHC and/or flow cytometry for more detailed characterization of immune cell population subsets / additional immune markers (e.g. IDO, CD4, CD3, FOXP3);
d. Immunohistochemistry for mismatch repair (MMR) proteins, SPARC and hENT1 expression;
e. Immunohistochemistry for MCT4 to determine correlation with immune marker expression and prognosis;
f. Tumour gene expression subtyping by RNA sequencing of laser capture microdissected biopsy tumour component;
g. Gene expression analysis (NanoString nCounter gene expression system) of immune-related genes;
h. Genomic instability measured by MSI assays or using SNP arrays.

Directions:

Within 4 weeks of randomization of the patient, an original tumour block should be sent to the CCTG Pathology Coordinator. Centres should contact the CCTG Study Coordinator and/or the Pathology Coordinator if they are unable to submit a tumour block, as sufficient tissue is required for the assays described below.

Complete the EDC Archival Tumour Tissue Submission Form. Print a copy of the completed form and ship tumour blocks/slides along with a Request for Payment form to:

Shakeel Virk
Pathology Coordinator Canadian Cancer Trials Group
Richardson Labs Bldg, 4th Floor
88 Stuart St.
Queen's University
Kingston, ON K7L 3N6
Tel: 613-533-2906 / Fax: 613-548-2486
Email: virks@queensu.ca

12.2 Week 8 On-treatment Biopsy (Optional)

The collection of additional biopsy to tissue collection at 8 weeks after start of treatment is optional for sites. Participating sites should present the option of the additional to all patient for whom participation is also optional.

Planned priority assays on biopsied tumour tissue include:

a. Immunohistochemistry for PD-L1 and CTLA-4 expression

b. Immunohistochemistry for tumour infiltrating lymphocytes (CD8+ T cells)

c. Other exploratory analysis by IHC and/or flow cytometry for more detailed characterization of immune cell population subsets / additional immune markers (e.g. IDO, CD4, CD3, FOXP3)

d. Immunohistochemistry for MMR, SPARC and hENT1 expression

Detailed instructions for FFPE sample acquisition, preparation, and shipping are found in the PA.7 Lab Manual.

12.3 Blood, Serum and Plasma Collection (Mandatory)

The CCTG is interested in exploring the use of surrogate tissues such as serum and plasma in evaluating potential prognostic or predictive biomarkers. Blood, serum and plasma samples will be collected and banked for planned studies from all patients after randomization but before the first dose of study treatment, at 8 weeks after randomization and at progression (if not already done).

Planned priority assays on blood, serum and plasma include:

- Circulating tumour DNA;

Detailed instructions for blood, serum and plasma sample acquisition, preparation, and shipping are found in the PA.7 Lab Manual.

12.4 Optional Banking of Samples

Banking of Tumour Tissue:

Mandatory submission of tumour tissue has been described above. The subsequent banking of collected diagnostic tissue is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Blocks and blood will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

After patient consent, collection of paraffin tumour blocks will preferred, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If tumour blocks are unavailable, then two x 2 mm cores of tumour from the block and 30 specimen slides are preferred. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval.

Banking of Blood, Serum, and Plasma:

Mandatory submission of whole blood, serum, and plasma has been described above. The subsequent banking of collected samples is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Samples will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

The primary objective of this phase II randomized study is to assess the effect of the addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel on the Overall Survival in patients with metastatic pancreatic cancer. Secondary objectives include assessments of Progression Free Survival, Objective Response Rate, and Adverse Events.

Prior to starting the randomized component of the study, 10 additional patients will be accrued to Arm 2 (gemcitabine + nab-paclitaxel+ durvalumab + tremelimumab) in a safety run-in to evaluate the safety and tolerability of the combination. Provided that Arm 2 is deemed safe and tolerable after the review of data from the safety run-in, then after stratification by ECOG performance status (0 *versus* 1) and receipt of prior adjuvant therapy (yes *versus* no), patients will be randomized in a 2:1 ratio to the following two arms: addition of durvalumab + tremelimumab to the standard 1st line chemotherapy with gemcitabine/nab-paclitaxel (Arm 2), and standard 1st line chemotherapy with gemcitabine + nab-paclitaxel (Arm 1).

13.2 Primary Endpoints and Analysis

Overall Survival

Overall Survival, the primary endpoint of this study, is defined as the time from randomization to death from any cause. Patients who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive. Patients will be analyzed in the arm to which they are randomized regardless of the treatment they received (intent-to-treat analysis). The survival experience of patients in three treatment groups will be summarized by the Kaplan-Meier method and compared primarily by a stratified log-rank test adjusting for the stratification variables (ECOG performance status and receipt of prior adjuvant therapy) at randomization. Secondary analyses based on stratified Cox proportional hazards model will also be performed. ECOG performance status (0 versus 1) and receipt of prior adjuvant therapy (yes versus no) will be the stratification factor to define the stratified Cox proportional hazards model. Besides the treatment factor (combination of durvalumab and tremelimumab + BSC versus BSC alone), the following factors at patient entry will be included in the stratified Cox proportional hazards model:

- Age (< 65 versus ≥ 65);
- Sex (male versus female);
- Number of organ sites involved at baseline (≤ 2 versus > 2).

A formal pre-planned subset analysis for the primary endpoint (OS) will be conducted to address the benefit of addition of durvalumab + tremelimumab to standard 1st line chemotherapy with gemcitabine/nab-paclitaxel between the groups defined by the above factors and the following:

- ECOG Performance Status (0 versus 1);
- Race (white, black, Asian, other).

Progression-Free Survival

Progression-Free Survival (PFS) is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last tumour assessment. This includes patients who are lost to follow-up or have withdrawn consent. All analyses for OS will also be performed for PFS, using similar methodology. A sensitivity analysis of PFS will also be performed where PFS is defined as the time from randomization to the second documentation of unequivocal disease progression in those patients who continued study therapy beyond the first objective documentation of disease progression and with interim CR, PR or SD documented.

Objective Response Rate

Objective Response Rate (ORR) is defined as the proportion of patients with a documented complete response and partial response based on RECIST 1.1. The primary estimate of ORR will be based on all patients randomized. A Cochran-Mantel-Haenszel test adjusting for the stratification factor (ECOG performance status) at the time of randomization will be used as the primary method to compare the objective response rates. A sensitivity analysis of ORR will also be performed where response is defined as the proportion of patients with a documented complete response and partial response based on RECIST 1.1 and/or Immune-Related Response Criteria (irRECIST) .

Safety Analysis

All patients who have received at least one dose of protocol treatment will be included in the safety analysis. The incidence of adverse events will be summarized by type of adverse event and severity using the NCI Common Terminology Criteria for Adverse Events. A Fisher's exact test will be used to compare adverse events between the two arms if required.

13.3 Sample Size and Duration of Study

The 10 patients registered in the safety-run in will not be included in the overall sample size.

The study is designed to have a power of 80% and a two-sided alpha of 10% to detect a 35% reduction in the continuous risk of death (HR 0.65, which corresponds to an increase of median survival from 8.5 to 13.1 months). It is estimated that 150 events will be required to detect this reduction. The final analysis will be performed when 150 events are observed. Assuming an average accrual rate of 10 patients per month, the required number of events would be observed by accruing a total of 180 patients and following them for an additional 17 months. The estimated total duration of the study would be 35 months.

13.4 Safety Monitoring

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

13.5 Interim Analysis

No interim analysis will be performed.

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 (CCTG) 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.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.

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

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

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

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

15.3 Obtaining Informed Consent

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

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

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

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

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

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

15.3.1 *Obtaining Consent for Pregnancy*

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

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

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

Obtaining Consent for Research on Children

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

15.4 Discontinuation of the Trial

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

If this trial is discontinued at anytime 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.

AstraZeneca has reserved the right to audit participating centres. Audits may only be conducted after consultation with CCTG.

15.8 Case Report Forms

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

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the PA.7 area of the CCTG web-site (http://www.ctg.queensu.ca/trials/gi/PA7/PA7.html).

16.0 REFERENCES

Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, and Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumour-associated T cells. Clin Cancer Res. 2011. 17(13):4232-4244

Antonia SJ, Brahmer JR, Gettinger SN, Chow LQM, Juergens RA, Shepherd FA, Laurie SA, Gerber DE, Goldman JW, Shen Y, Harbison C, Alaparthy S, Chen AC, Borghaei H, Rizvi NA. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) or erlotinib (ERL) in advanced non-small cell lung cancer (NSCLC) Abstract presented at the European Society for Medical Oncology (ESMO) Annual Meeting, Madrid, Spain, September 26–30, 2014.

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

Antonia SJ, Goldberg SB, Balmanoukian AS et al. Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. J Clin Oncol 33, 2015 (suppl; abstr 3014).

Antonia SJ, Bendell J, Taylor M, et al. Phase I/II study (CheckMate 032) of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC). J Clin Oncol 33, 2015 (suppl; abstr 7503).

Apetoh L, Tesniere A, Ghiringhelli F et al. Molecular interactions between dying tumour cells and the innate immune system determine the efficacy of conventional anticancer therapies. Cancer Res 2008; 68: 4026-4030.

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

Brusa D, Serra S, Coscia M, Rossi D, D'Arena G, Laurenti L, et al. The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia. Haematologica. 2013 Jun; 98(6):953-963.

Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15:2403-13.

Eisenhauer E, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline version 1.1. Eur J Can 45: 228-47, 2009.

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

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

Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumour-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Nat Acad Sci U S A. 2007;104(9):3360-5.

Holm, S. 1979. A simple sequential rejective multiple test procedure. Scandinavian Journal of Statistics 6:65-70

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.

Khleif S, Lutzky J, Segal N et al. MEDI4736, an anti-PD-L1 antibody with modified Fc domain: preclinical evaluation and early clinical results from a phase I study in patients with advanced solid tumours. (Abst 802) European Cancer Congress 2013, Amsterdam, Netherlands Sept 27-Oct 1, 20

Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al. Survivin and B7-H1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. Clin Cancer Res. 2007;13(6):1749-56.

Loos M, Giese NA, Kleeff J, Giese T, Gaida MM, Bergmann F, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic adenocarcinoma. Cancer Lett. 2008;268(1):98-109.

Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol. 2012; 30(17):2046-54.

Makuch, R.W. and Simon, R.M., Sample size requirements for comparing time-to-failure among k treatment groups, J. Chron Dis. 1982; 35:861-867.

Merritt RE, Mahtabifard A, Yamada RE et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumour immunity in poorly immunogenic murine lung cancer. J Thoracic Cardiovascular Surg 2003; 126: 1609-1617.

Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumour cells immune escape through suppressing tumour infiltrating dendritic cells maturation. Med Oncol. 2011 Sep;28(3):682-8.

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, Nakamura S, Enomoto K, Yagita H, Azuma M, Nakajima Y. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007; 13(7):2151-2157.

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

Park JJ, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, Yao S, Tsushima F, Narazaki H, Anand S, Liu Y, Strome SE, Chen L, Tamada K. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance**.** Blood 2010; 116(8):1291-1298.

Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013;24:75-83.

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

Stewart RA, Morrow M, Chodorge M et al. Abstract LB-158. MEDI4736: Delivering effective blockade of immunosuppression to enhance tumour rejection: monoclonal antibody discovery and preclinical development. Cancer Research 2011; 71(8 suppl 1): Abstract nr LB-158. Proceedings: AACR 102nd Annual Meeting 2011-April 2-6, 2011, .Orlando, FL.

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

Thompson RH, Webster WS, Cheville JC, Lohse CM, Dong H, Leibovich BC, Kuntz SM, Sengupta S, Kwon ED, Blute ML. B7-H1 glycoprotein blockade: A novel strategy to enhance immunotherapy in patients with renal cell carcinoma **.** Urology 2005; 66 (Supplement 5A): 10-14.

Thompson RH, Kwon ED. Significance of B7-H1 Overexpression in Kidney Cancer. Clinical Genitourinary Cancer 2006; 5(3): 206-211.

Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical Significance of B7-H1 and B7-1 Expressions in Pancreatic Carcinoma. World Journal of Surgery 2010; 34(5): 1059-1065.

Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369(2):122-33.

Venook AP, Egorin MJ, Rosner GL, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. J Clin Oncol 2000; 18:2780-7.

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nature Reviews Immunology 2008; 8.6:467-477.

APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

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

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

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

APPENDIX II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Details of Drug Distribution, Supply and Control/Accountability are provided in the *PA.7 Drug Supply Manual*, available on the PA.7 website (http://www.ctg.queensu.ca/trials/gi/PA7/PA7.html).

Distribution

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

Nab-paclitaxel and Gemcitabine are commercially available and will not be supplied.

Initial Supply

BARL will ship durvalumab and tremelimumab directly to the site pharmacy. Sites should follow instruction RE initial supply in the PA.7 Drug Supply Manual. Sites should allow 5 working days for initial drug shipments to arrive.

Resupply

For re-supply of durvalumab and tremelimumab, sites should follow instruction in the *PA.7 Drug Supply Manual*. Sites should allow 5 working days for re-supply shipments 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 and for the disposition of the product (Drug Accountability Log, available on the PA.7 website (http://www.ctg.queensu.ca/trials/gi/PA7/PA7.html). 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 of Expired Medication

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

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 REGISTERED ON THIS STUDY

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

APPENDIX III - DOSING 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) 1Nov2017 Version

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

https://www.ctg.queensu.ca/docs/trials/generic_forms/DoseMod-ToxMngmtGuidelines/DoseMod-ToxicityMgmntGuidelines_01Nov2017.pdf

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

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

The ELECTRONIC CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required at	To be completed electronically	Supporting Documentation Required[1]
Eligibility Checklist	Prior to randomization	At the time of randomization	Consent form[2] Pathology/cytology report(s) Operative report(s) Radiology reports (including CT chest/abdomen/pelvis) Tumour Measurement Worksheet
Baseline Report	At the time of randomization	Within 2 week of randomization	
Correlative Studies Report (Tumour and Blood)	Continuous running-log folder See Sections 6.0 and 12.0	Information pertaining to tumour tissue submission must be completed as soon as possible after randomization, and tissue submitted within 4 weeks of randomization Information pertaining to **baseline/pretreatment** (i.e. tumour specimen information and blood collection for correlative studies) must be completed within 2 weeks of randomization. Information pertaining to **post randomization** blood collection samples (i.e. whole blood, plasma, and serum) for correlative studies and banking should be completed within 2 weeks after collection of final blood specimen. Information pertaining to the optional tumour biopsy (at 8 weeks, for consenting patients) must be completed as soon as possible at tissue submitted within 4 weeks of biopsy.	Consent form[2] Diagnostic pathology report *(for tumour tissue only)*
Concomitant Medication Report	Continuous running-log folder		
Treatment Report	Every cycle (28 days) while patient is on protocol treatment	Within 2 weeks of the end of each cycle	*If applicable:* CT chest/abdomen/pelvis report(s) Other radiology reports Tumour Measurement Worksheet ECG report
End of Treatment Report	To be completed once when the patient goes off all protocol treatment permanently	Within 2 weeks of the end of treatment	
Post Treatment Follow-up Report	To be completed once on all patients, 4 weeks post-protocol treatment discontinuation	Within 2 weeks of the 4 week post-treatment visit	*If applicable:* CT chest/abdomen/pelvis report(s) Other radiology reports Tumour Measurement Worksheet

table continued on next page ...

Electronic Folder	Required at	To be completed electronically	Supporting Documentation Required[1]
Follow-up Report	Every 3 months after the 4-week post-treatment visit, until PD	Within 2 weeks of follow-up visit	CT chest/abdomen/pelvis report(s) Other radiology reports Tumour Measurement Worksheet
Relapse/Progression Report	Upon the patient's objective disease progression	Within 4 weeks of disease progression	Relevant radiology, operative and pathology reports
Short Follow-up Report	Every 3 months after the 4-week post-treatment visit, after PD	Within 2 weeks of follow-up visit	
Death Report	When patient dies	Within 4 weeks of patient's death	Autopsy/post-mortem report, if done
SAE Report[3]	At the time of the event	Within 1 working day[3]	

1 Please scan and upload all required source documentation into the EDC Supporting Document Upload Tool. Ensure the patient's identifiers (e.g. name) are blacked-out on all source documentation.

2 For Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated.

3 See section 11.0 Serious Adverse Event Reporting for details.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

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

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

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

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

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

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

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

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

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

1. Preamble

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

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

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

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

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

2. Pretreatment Assessment

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

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

3. Assessments During Treatment

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

4. Assessments During Follow-up

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

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

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

5. What If . . .

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

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

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

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

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

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

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

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

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

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

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

6. Waiving the Quality of Life Component

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

7. Unwillingness to Complete Quality of Life Questionnaire

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

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

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

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

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **PA.7**

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

Patient Information

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

Institution: _____ Investigator: _____

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

☐ Prior to randomization (with 14 days prior to randomization)

During protocol treatment:

☐ 4 weeks ☐ 8 weeks ☐ 12 weeks ☐ 16 weeks ☐ 24 weeks

Then every 3 months until PD or the initiation of another chemotherapy treatment

☐ 3 months ☐ 6 months ☐ 9 months ☐ 12 months ☐ 15 months ☐ 18 months ☐ 21 months

☐ 24 months ☐ ___ months

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

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

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

Comments: _____

_____

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

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

CCTG use only

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

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

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (PA.7)

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

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

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

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

Please go on to the next page

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

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

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

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

1	2	3	4	5	6	7
Very Poor						Excellent

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

1	2	3	4	5	6	7
Very Poor						Excellent

Please check to make sure you have answered all the questions.

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

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

Thank you.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to allocation.	Julia Baran or Vicki Classen Clinical Trials Assistants, CCTG Email: jbaran@ctg.queensu.ca vclassen@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Barbara Graham or Lisa Gallinaro Study Coordinators, CCTG Email: bgraham@ctg.queensu.ca lgallinaro@ctg.queensu.ca or: Dr. Chris O'Callaghan Senior Investigator, CCTG Email: cocallaghan@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr.Dan Renouf Study Chair Email: drenouf@bccancer.bc.ca		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Chris O'Callaghan Senior Investigator, CCTG or: Barbara Graham Study Coordinator, CCTG	613-533-6430	613-533-2941
DRUG ORDERING See Appendix II for full details.	See Appendix II and trial website: http://www.ctg.queensu.ca/trials/gi/PA7/PA7.html for details and contact information		
ELECTRONIC DATA CAPTURE (EDC) AND RIPPLE (technical support)	CCTG Home Page (Toolbox): https://scooby.ctg.queensu.ca Email Support Staff at: support@ctg.queensu.ca		