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CANADIAN CANCER TRIALS GROUP (CCTG)

A RANDOMIZED TRIAL OF DURVALUMAB AND TREMELIMUMAB ± PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH METASTATIC (STAGE IV) SQUAMOUS OR NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

CCTG Protocol Number: BR.34

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SUPPORTED BY:	AstraZeneca

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

CONFIDENTIALITY STATEMENT

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

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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 CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to 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 CCTG and AstraZeneca and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified / Principal Investigator
(printed name and signature)

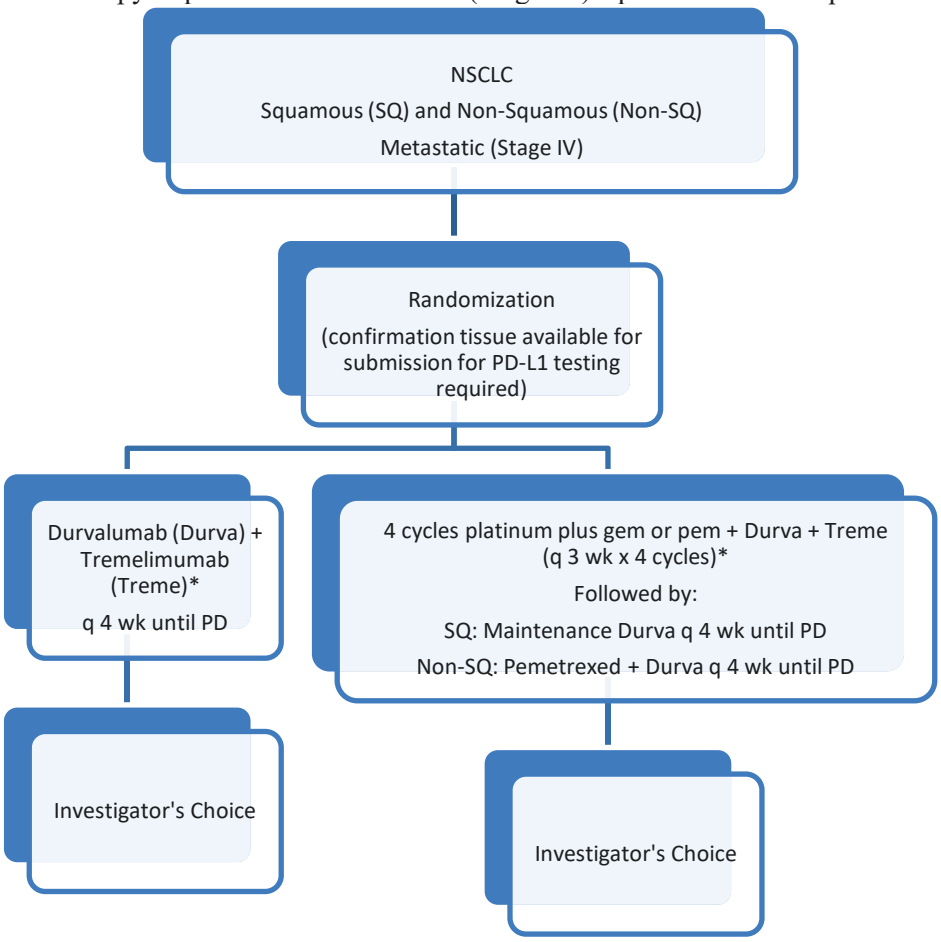
Date

Protocol Number: CCTG BR.34

CENTRE: _____

TREATMENT SCHEMA

This is an international, multicenter, prospective 2-arm randomized trial of durvalumab and tremelimumab ± platinum chemotherapy in patients with metastatic (Stage IV) squamous or non-squamous NSCLC.



* dosing:
- Tremelimumab will be given for total of 4 doses.
- Durvalumab 1500 mg/Tremelimumab 75 mg
- Maintenance Durvalumab in the chemotherapy arm starts at week 12.

Stratification:
- Squamous vs non-squamous
- IVA vs. IVB
- smoking status (< 100 cigarettes vs previous vs current)

Sample Size: 300

All patients will be followed for progression (RECIST and iRECIST) and death.

1.0 OBJECTIVES

This is an international, multicenter, prospective 2-arm, randomized trial of durvalumab and tremelimumab ± platinum-based chemotherapy in metastatic (Stage IV) squamous and non-squamous NSCLC. Patients will be randomized to durvalumab and tremelimumab alone or durvalumab and tremelimumab plus platinum-based chemotherapy.

1.1 Primary Objective

- To compare the overall survival (OS) of patients receiving durvalumab, tremelimumab plus platinum-based chemotherapy to that of patients receiving durvalumab and tremelimumab alone.

1.2 Secondary Objectives

- To compare progression free survival (PFS; RECIST 1.1) at 1 year between arms;
- To compare objective response rate (ORR; RECIST 1.1 and iRECIST) between arms;
- To compare Quality of Life (QoL) between arms;
- To evaluate the nature, severity, and frequency of toxicities between arms;
- To evaluate the incremental cost effectiveness and cost utility ratios between arms;
- To correlate the expression of tissue (including PD-L1) and blood markers with outcomes and response.

1.3 Exploratory Objectives

- To evaluate the correlation between aberrations detected using genomic cell-free DNA in blood and outcomes;
- Progression free survival as defined by iRECIST.

2.0 BACKGROUND INFORMATION AND RATIONALE

Emerging data suggest that PD-1/PD-L1 inhibitors benefit some patients with advanced metastatic NSCLC. In some patients, such as those with tumours which have high expression of PD-1, the benefit may be superior to chemotherapy in both the first and second line settings. The addition of anti-CTLA4 to PD-1/PD-L1 inhibitors may increase activity especially for tumours with low or no PD-L1 expression. Recently reported trials suggest that adding PD-1/PD-L1 inhibitors to or combination chemotherapy may provide greater benefit *[Langer 2016]* randomized phase III trials are underway. A key question is whether chemotherapy combined with dual immunotherapy will provide greater benefit than immunotherapy alone (dual or single) while retaining acceptable tolerability and safety compared to sequencing these therapies.

We plan to conduct a proof-of concept 2-arm, randomized study to test whether first line platinum-based combination chemotherapy combined with the PD-L1 inhibitor durvalumab plus the anti-CTL14 inhibitor tremelimumab, can improve outcomes in patients most at risk "poorer-prognosis patients" receiving first-line therapy for advanced or metastatic NSCLC, compared to doublet immunotherapy alone. Poor prognosis is defined as Stage IV disease according to the 8th TNM version staging. The primary endpoint is overall survival. In addition, we will evaluate biomarkers predictive of treatment benefit, impact on health related quality of life and cost analysis.

2.1 Non-Small Cell Lung Cancer

Non-Small Cell Lung Cancer (NSCLC) remains the most commonly diagnosed and most lethal malignancy in Canada and worldwide *[Siegel 2013; Canadian Cancer Statistics 2015]*. The majority of patients with NSCLC present with advanced/metastatic disease. Non-squamous NSCLC accounts for 75% of all NSCLC, and squamous NSCLC accounts for the remaining 25% *[Silva 2016]*. Up to two thirds of NSCLC present with locally-advanced or advanced disease that is not amenable to surgery. In such patients, platinum-based chemotherapy doublets have been shown to improve symptoms, delay disease progression and improve overall survival to a median of 10 months *[Travis 2011]*. Until recently, cytotoxic chemotherapy has been considered the standard of care for good performance patients with advanced NSCLC in the first and second line setting *[Reck 2016; Herbst 2016; Borghaei 2015; Brahmer 2015]*.

Non-squamous NSCLC

First-line platinum-pemetrexed chemotherapy doublet is used for molecularly unselected non-squamous NSCLC and is associated with a 12.6 months and 5.3 months benefit in overall survival and disease free survival, respectively *[Scagliotti 2008]*. More recently, studies have shown platinum-based pemetrexed combinations offer superior outcomes for patients with adenocarcinoma, as does pemetrexed maintenance therapy *[Ciuleanu 2009; Paz-Ares 2012; Scagliotti 2014]*. Currently, maintenance treatment in selected NSCLC patients with pemetrexed (with non-squamous histology) is given, although associated with modest improvements in survival and quality of life. When compared to placebo, pemetrexed was statistically superior in DFS (4.4 months vs 2.8 months; p,0.001), and in OS (16.9 months vs 14.0 months; p=0.019) *[NSCLC Meta-Analyses Collaborative Group 2008; Ciuleanu 2009; Capuzzo 2010; Paz-Ares 2013]*.

In patients with non-squamous NSCLC an additional modest benefit over that of standard combination chemotherapy, with the addition of the anti-angiogenic agent bevacizumab *[Sandler 2006]* or the epidermal growth factor (EGFR) inhibitor cetuximab has been reported *[Pirker 2009]*, although these agents are not widely used because of perceived lack of cost-benefit.

For patients with EGFR sensitizing mutation OR ALK fusion positive disease, first- line therapy with an EGFR (gefitinib or erlotinib) or ALK (crizotinib) TKIs, respectively, is associated with a superior progression free survival compared with first-line cytotoxic chemotherapy and has become a standard first-line approach *[Fukuoka 2011; Rosell 2012; Shaw 2013]*. Despite these advances, the majority of patients with NSCLC die of their disease.

Squamous NSCLC

Platinum-based chemotherapy has also been the standard of care for squamous NSCLC, and may include gemcitabine or taxanes. In a randomized trial comparing two different chemotherapy regimens, cisplatin/gemcitabine was associated with improved OS and PFS when compared to cisplatin/pemetrexed; both analyses were statistically significant in favor of the gemcitabine arm. *[Scaglotti 2008]*. Response rates have been reported in the range of 23-30%, and thrombocytopenia and fatigue are side effects that can lead to treatment discontinuation *[Langer 2016]*. Although generally well-tolerated, the long-term prognosis of patients with advanced squamous NSCLC remains poor.

Immune Check-point Inhibitors

Recent advances in the understanding of immune pathways within the tumour microenvironment have led to the identification of immune-checkpoint inhibitors as promising therapeutics in solid malignancies, including NSCLC *[Brahmer 2010; Pardoll 2012; Soria 2015]*.

Programmed death 1 (PD-1) protein is a co-inhibitory receptor known to be expressed on activated T-cells, which when bound to its ligand PD-L1, limits T-cell antitumour activity in the tumour microenvironment *[Fife 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]*. 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 *[Iwai 2002]*.

CTLA-4 is a co-inhibitory receptor expressed on activated T-cells and regulates early stage T-cell activation, reducing its amplitude. Tremelimumab is a human IgG2 monoclonal antibody directed against the T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) *[Tarhini 2013]*. Tremelimumab binds to CTLA-4 and blocks the binding of the antigen-presenting cell ligands B7-1 and B7-2 to CTLA-4, resulting in inhibition of B7-CTLA4-mediated downregulation of T-cell activation. A phase II trial of tremelimumab in patients with chemotherapy-resistant mesothelioma, the primary endpoint for efficacy was not reached *[Calabro 2013]*.

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, lung and bladder cancers *[Pardoll 2012; Brahmer 2012; Garon 2015; Hahn 2015]*. In patients with recurrent or metastatic, platinum-refractory squamous cell carcinoma of the head and neck, nivolumab showed an improvement in mOs of over 2 months when compared to physician choice *[Ferris 2016]*. In the same population, pembrolizumab reported an overall response rate (ORR) of 17.7% in a non-selected population *[Mehra 2016]*. In bladder cancer, single agent Atezolizumab has been granted fast track FDA approval after demonstrating an ORR of 15% when compared to 10% offered by chemotherapy *[Rosenberg, 2016]*. PD-1 inhibitors pembrolizumab and nivolumab have been approved for the treatment of squamous and non-squamous NSCLC (after failure of platinum-based chemotherapy) and are under evaluation in combination *[Hodi 2010; Sharma 2011; Brahmer 2012; Topalian 2012; Brahmer 2015; Borghaei 2015; Garon 2015]*. In the first-line setting, pembrolizumab has been reported to improve DFS and OS when compared to chemotherapy in patients with PD-L1 ≥50% *[Reck 2016]*; however, nivolumab was not superior to chemotherapy *[Socinski 2016]*. This is changing the landscape of first-line therapy in patients with NSCLC. Single agent immunotherapy with anti-PD-1 or anti-PD-L1 antibodies has been generally well tolerated with grade 1 or 2 fatigue, diarrhea, rash, pruritus, nausea and decreased appetite commonly reported. Immune-related adverse events are uncommon (<2%), and include pneumonitis, vitiligo, colitis, hepatitis and hypophysitis and thyroiditis *[Antonia 2014]*.

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]*. In a phase I dose escalation study in advanced solid tumours evaluating doses (0.1-15.0 mg/kg every 2 weeks (q 2wk) or 3 weeks (q 3wk)), signals of durable clinical activity have been observed in NSCLC. A phase 1b study combining durvalumab with tremelimumab in patients with advanced NSCLC also demonstrated antitumour activity regardless of PD-L1 status *[Antonia 2016]*. Results of early trials with durvalumab ± tremelimumab in advanced cancers are consistent with a class effect of early and sustained tumour control that has been observed previously with other inhibitors of the immune checkpoint pathway. Evidence of clinical activity was noted both in patients with PD-L1-positive tumours and in those with PD-L1-negative tumours. More recently, durvalumab has reported an ORR 31% in bladder cancer and remarkably all patients that showed effect from the intervention expressed PD-L1 in ≥ 25% of tumour or inflammatory cells *[Massard 2016]*. The combination of durvalumab and tremelimumab is tolerable at doses of durvalumab 20 mg q 4wk and tremelimumab 1 mg/kg q 4wk. Higher doses did not result in greater antitumour activity but were generally associated with higher rates of adverse events (AEs).

The MYSTIC trial [NCT02453282] is a phase III trial comparing durvalumab with or without tremelimumab versus chemotherapy in previously untreated patients with advanced/metastatic NSCLC. The primary endpoints for this trial are PFS, OS and PFS in patients PD-L1-postive (PD-L1 ≥ 50%). The total sample size of 1092 patients, has been recruited and results are expected during Q2 2017. This study supports our dual immunotherapy arm as an arm of this proof of concept trial.

Despite these exciting data, many patients do not derive benefit from PD-1/PD-L1 inhibitors. Combinations of immune checkpoint inhibitors targeting separate immune pathways are currently being investigated in patients with a number of cancers including in NSCLC *[Antonia 2015; Patnaik 2015]*. In melanoma, combinations of ipilimumab (a CTLA-4 checkpoint inhibitor) with nivolumab (a PD-1 checkpoint inhibitor) are more active compared to ipilimumab alone, with higher response rates and longer progression free survival [*Larkin 2015; Postow 2015]*. In advanced NSCLC, inhibition of the PD-L1/PD-1 immune checkpoint pathway induced durable clinical responses across all histologies *[Silva, 2015]*. Combinations with CTLA-4 inhibitors are particularly promising, with superior efficacy in other tumour types such as melanoma and SCLC. A study combining nivolumab with ipilimumab in NSCLC showed durable responses in patients with PD-L1 negative as well as PD-L1 positive tumours *[Rivzi 2016]*.

Immune checkpoint inhibitors and chemotherapy

While immune checkpoint inhibitors have shown clear activity and benefit, their optimal usage, including combinations, setting and sequence, in patients with NSCLC is not yet defined. Combination therapy including platinum-based chemotherapy and immune check-point inhibitors is an intriguing therapeutic approach. In preclinical models, conventional platinum-based chemotherapy has been shown to induce T-cell activation through the release of tumour-specific antigens during cancer cell death *[Apetoh 2008; Merritt 2003]*. Clinical trials to date suggest combinations of immune therapy and chemotherapy are tolerable and active *[Langer 2016].*

Although chemotherapy is generally thought to suppress the immune system, chemotherapy can promote tumour immunity *[Emens 2015]*. Generation of an effective antitumour immune response requires several functional steps: availability of tumour antigen in the correct context (usually immunogenic cell death or ICD); uptake of antigen by antigen presenting cells (APCs): APC activation and antigen cross-presentation to T-cells; infiltration of T-cells into the tumour; minimal suppressive activity from KDSC and Treg; and continued cytotoxic activity of T-cells against tumour cells without exhaustion induce by negative regulatory checkpoints *[Pardoll 2012]*. In tumour models, gemcitabine, a nucleoside analog that inhibits DNA replication, changes the cellular composition of the tumour microenvironment, by synergistically increasing MDSC and of CD8 T-cells within tumours *[Ko 2007; Nowak 2003]*. In addition, chemotherapeutics can change the cytokine profile and block T regulatory cell function suppressing tumour immune cell response. Some chemotherapies, such as paclitaxel, can induce PD-L1 expression. In preclinical models, conventional platinum-based chemotherapy has been shown to induce T-cell activation through the release of tumour-specific antigens during cancer cell death *[Apetoh, 2008; Merritt, 2006]*. Based on these studies and others that show tumour-infiltrating T-cells are found in some histologies of NSCLC *[Hiraoka 2006; Ruffini 2009]* combination chemotherapy with checkpoint inhibitors is a rational therapeutic approach to upfront management of NSCLC to improve clinical efficacy.

A randomized phase 2 study published in 2012 reported superior immune-related PFS (ir-PFS) when ipilimumab (CTLA-4 antibody) was added to carboplatin and paclitaxel (started at cycle 3). More recently, a study combining the anti-PD-1, pembrolizumab with carboplatin and paclitaxel or pemetrexed, showed a significant improvement in overall-response-rate (ORR) for the combination arm; increasing response rate from 30% with chemo alone to 67% when immunotherapy was added. *[Papadimitrakopoulou 2015; Lynch 2012; Langer 2016]*. Canadian Cancer Trials Group is testing durvalumab ± tremelimumab in patients receiving combination chemotherapy including pemetrexed and cisplatin / carboplatin. The combination appears tolerable with full doses of the chemotherapy agents and durvalumab, and either 1 or 3mg/kg of tremelimumab.

High-risk population of advanced NSCLC patients

Given the anticipated increase in toxicity, complexity of treatment and cost, we propose to evaluate the combination of dual immunotherapy and combination platinum chemotherapy in patients least likely to experience improved survival from a single agent PD-L1 inhibitor or standard cytotoxic therapy. For the purpose of this trial, poor prognosis is defined as stage IV disease according to the 8th TNM version staging. Distant metastasis are split into three categories: a) M1a defined as separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion. b) M1b defined as single extrathoracic metastasis; and c) M1c defined as multiple extrathoracic metastases in one or more organs.

Correlative Studies and Biomarkers

The identification of robust predictive biomarkers is particularly important for immunotherapies. Immune-based therapies are associated with significant toxicity in some patients, not all patients will derive benefit and the costs of the drugs are considerable. There is evidence that benefit from anti-PD-1/PD-L1 therapy is positively correlated with PD-L1 expression by immunohistochemistry *[Garon 2015]*. The evaluation of PD-L1 expression in tumour samples is planned for all patients. To prevent undue delay in the start of first-line chemotherapy treatment, patients will be registered, and will be randomized once tumour tissue for PD-L1 assay has been submitted. Other assays are planned for consenting patients, including genomic sequencing and mutational load (tumour tissue and cfDNA from blood).

Quality of Life

The assessment of Quality of Life (QoL) in all patients is an important aspect in this trial. The addition of two immune based therapies to standard platinum based chemotherapy may have positive (if increased activity) or negative effects (if increased toxicity) on patient well-being. Potential survival gains from new therapies in combination with standard therapy need to be assessed in terms of their QoL impact as incremental toxicity, especially immune mediated toxicities such as colitis, pneumonitis or endocrinopathies or pseudoprogression may adversely impact patient well-being. Thus, a patient perspective of the impact of treatment is an essential part of this study.

The EORTC core QoL questionnaire (QLQ-C30) *[Aaronson 1993]* and lung cancer module (QLQ-LC13) *[Bergman 1994]* will be used in this trial. Both are well-validated questionnaires that have been adapted for multiple languages, which is essential for this multinational study *[Earle 2004].* QoL outcomes from this study may be compared to other clinical trials performed by the Canadian Cancer Trials Group that used the EORTC instruments. The EORTC QLQ-C30 and QLQ-LC13 include items that address the main side effects of chemotherapy as well as durvalumab and tremelimumab.

Additional relevant questions will be appended to the EORTC instruments from the Canadian Cancer Trials Group Quality of Life Item Bank. These will relate to potential side effects of immune checkpoint inhibitors not assessed by the QLQ-C30 and QLQ-LC13; specifically, pruritus, rash and visual disturbance.

Health Economics

The adoption and governmental/third party payer funding of new cancer therapeutics is dependent on the demonstration of cost effectiveness. Therefore, accurate prospective economic data for any new therapeutic is critical to assist decision makers regarding funding issues.

A prospective economic evaluation will be conducted in selected participating centres to determine the incremental cost-effectiveness and cost-utility of adding standard platinum combination chemotherapy to immunotherapy in advanced/metastatic NSCLC from a government payer perspective, by prospectively collecting economic and resource utilization information during the trial. As part of the economic evaluation in this study, patient preferences, or utilities, will be measured using the EQ-5D questionnaire *[Brooks 1996]*. The EQ- 5D self-administered questionnaire consists of two pages comprising the EQ-5D descriptive system and the EQ Visual Analogue Scale (VAS). The EQ-5D descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension comprises five levels (no problems, slight problems, moderate problems, several problems and extreme problems). A unique EQ-5D health state is defined by combining one level from each of the five dimensions. The VAS records the respondent's self-rated health status on a vertical graduated (0-100) visual analogue scale. The EQ-5D is a validated instrument that has been used in population surveys and clinical trial settings. Analysis will be performed as detailed in the statistical section of the protocol (see Section 13).

In summary, preclinical and clinical data suggest that first line combination immunotherapy may benefit a broader cohort of patients with NSCLC while double immunotherapy plus standard combination chemotherapy appears to be very active. Evaluation of health related quality of life and costs of combining chemotherapy regimens with durvalumab and tremelimumab in this randomized proof of concept trial will not only inform health policy and practice, but will inform the design of a subsequent phase III trial.

3.0 BACKGROUND THERAPEUTIC INFORMATION

[redacted]

3.1.6 *Clinical Trials*

[redacted]

3.1.7 *Pharmaceutical Data - Durvalumab*

[redacted]

3.2 Tremelimumab

3.2.1 *Name and Chemical Information*

[redacted]

3.2.2 *Chemical Structure*

[redacted]

3.2.3 *Mechanism of Action*

[redacted]

3.2.4 *Experimental Antitumour Activity*

[redacted]

3.2.5 *Clinical Trials*

[redacted]

3.2.6 *Pharmaceutical Data - Tremelimumab*

[redacted]

[redacted]

3.3 Dosing of Durvalumab and Tremelimumab

[redacted]

[redacted]

[redacted]

3.4 Chemotherapy Regimens

[redacted]

[redacted]

4.0 STUDY POPULATION

Patients will have documented evidence of metastatic (Stage IV per 4.1.2) squamous or non-squamous NSCLC and be planned for standard first-line therapy.

4.1 Eligibility Criteria

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

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

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

4.1.1 Patients must have histologically and/or cytologically confirmed diagnosis of squamous or non-squamous, non-small cell carcinoma of the lung. Patients with poorly differentiated tumours will only be eligible if NSCLC is confirmed by immunohistochemistry markers (TTF1/P63 or P40/CK5). Patients with known sensitizing EGFR mutations or known ALK-fusion are not eligible.

4.1.2 Patients must have stage IV disease according to the 8th TNM version staging.

4.1.3 Patient must consent to provision of, and investigator(s) must confirm adequacy, of non-cytology tissue and 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 non-cytology tumour tissue in order that the specific correlative marker assays described in Section 12 (Correlative Studies) may be conducted.

Where adequate amount and quality of tissue exists but local centre regulations prohibit submission of blocks of tumour tissue, two 2 mm cores of tumour from the block and a predetermined number of slides of representative tumour tissue may be substituted. If this is also not permitted per local centre regulations, we will accept slides only. Any issues with respect tumour tissue submission must be discussed with CCTG prior to local activation of the centre. Failure to submit any tissue samples on request 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 excisional biopsy (fine needle aspirate is not adequate) of the primary or metastatic tumour will be required for the patient to be considered eligible for the study and must be done prior to randomization. Please refer to the BR.34 Correlative Studies Manual for details concerning adequacy of amount and quality of tumour tissue.

4.1.4 Patient must consent to provision of samples of blood in order that the specific correlative marker assays described in Section 12 (Correlative Studies) may be conducted.

4.1.5 All patients must have measurable disease as defined by RECIST 1.1 All radiology studies must be performed within 28 days prior to randomization (within 35 days if negative).

The criteria for defining measurable disease are as follows:

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

Measurable lesions must be outside a previous radiotherapy field if they are the sole site of disease, unless disease progression has been documented.

4.1.6 Patients must be 18 years of age or older.

4.1.7 ECOG performance status of 0 or 1. (See Appendix I).

4.1.8 *Laboratory Requirements*

Hematology	Absolute neutrophils	≥ 1.5 x 10^9/L
	Platelets	≥100 x 10^9/L
	Hemoglobin	≥ 90 g/L
Bio-chemistry	Bilirubin	≤ 1.5 x ULN (upper limit of normal)*
	AST and ALT**	≤ 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
	Serum creatinine and Creatinine clearance***	< 1.25 x ULN ≥ 45 mL/min

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

** It is preferable that both AST and ALT are assessed. For sites where only 1 of these parameters is routinely measured first and the other assessed if the first is abnormal, then either AST or ALT would be acceptable.

*** For patients with non-squamous histology, the creatinine clearance must be ≥ 45 ml/min. For patients with squamous histology, there is no lower limit.

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

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

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

4.1.9 *Prior Therapy*

Cytotoxic Chemotherapy:
Patients may not have received prior cytotoxic chemotherapy for advanced/metastatic disease.

Adjuvant Chemotherapy:
Patients may have had prior adjuvant therapy for completely resected disease, providing it has been completed at least 12 months prior to randomization.

Patients treated with concurrent chemotherapy/radiation regimens for unresectable locally advanced Stage III disease will be eligible providing it has been completed at least 12 months prior to randomization.

Other Systemic Therapy:
Patients may not have received prior EGFR or alk inhibitors. Patients may not have received prior treatment with immune-based therapy, including durvalumab and tremelimumab vaccines or oncolytic viral therapy.

Patients must have recovered from any reversible treatment related toxicities prior to randomization.

Radiation:
Prior external beam radiation is permitted provided a minimum of 14 days (2 weeks) have elapsed between the last dose of radiation and date of randomization. Concurrent radiotherapy is not permitted.

NOTE: For patients who receive radiation to the brain, a minimum of 28 days must have elapsed between the last dose of radiation and the date of randomization. This is to allow sufficient time to ensure that radiologic evidence of stable disease is observed prior to treatment (see ineligibility criterion 4.2.9).

Patients must have recovered from any acute toxic effects from radiation prior to randomization.

Surgery:
Previous surgery is permitted provided that wound healing has occurred and at least 14 days have elapsed (major surgery) prior to randomization.

4.1.10 Patient must be able (i.e. sufficiently fluent) and willing to complete the quality of life and health economics questionnaires. The baseline assessment must already have been completed. Inability (illiteracy, loss of sight, or other equivalent reason) 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.

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

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

4.1.12 Patients must be accessible for treatment and follow-up. All randomized patients must be followed and treated at participating centres. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Call the CCTG office at 613-533-6430 if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

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

4.1.14 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. 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.

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

4.2 Ineligibility Criteria

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

- Patients with alopecia.
- Patients with Grave's disease, vitiligo or psoriasis not requiring systemic treatment (within the last 2 years).
- Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement.

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

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

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

4.2.5 History of hypersensitivity to durvalumab or tremelimumab or any excipient. Patients who have received other treatment or other antibodies must not have had intolerable toxicity or required steroids to manage toxicity.

4.2.6 Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) $\geq$ 470 msec in screening ECG measured using standard institutional method or history of familial long QT syndrome.

4.2.7 Patients who have untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects). Patients with a significant cardiac history, even if now controlled, should have a LVEF $\geq$ 45%. (Note: patients with uncomplicated controlled hypertension do not require LVEF measurement in the absence of other significant cardiac history)

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

4.2.9 Patients with untreated brain or meningeal metastases are not eligible. Patients with treated CNS disease who have radiologic AND clinical evidence of stable brain metastases, with no evidence of cavitation or hemorrhage in the brain lesion, are eligible providing that they are asymptomatic and do not require corticosteroids (must have discontinued steroids at least 1 week prior to randomization).

4.2.10 *Pregnant or Lactating Women:*
Women of childbearing potential must have a pregnancy test (urine or serum) proven negative within 14 days prior to randomization. If urine test is positive, pregnancy testing may then 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. Men and women of child-bearing potential must agree to use adequate contraception as described in Section 9.3.1.

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

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

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)	Day 1 each cycle, and as clinically indicated	Days 1 & 8 cycle 1; then Day 1 subsequent cycles (unless clinically indicated)	6 weeks after baseline (during treatment)	Every 12 weeks after baseline (during treatment)	4 weeks after completion of protocol therapy[1]	Post-treatment[2]: Every 12 weeks until PD[3], then every 24 weeks until death
History and Physical Exam							
Including: height, weight, BSA, tobacco use, performance status,	X	X				X	X
Clinical tumour measurements (if applicable)	X	X		X	X	X[4]	X[4]
Blood pressure, heart rate, temperature	X	X[5]				X	
Concomitant Medications	X	X				X	
Laboratory Procedures/Assessments[6]							
CBC, differential, platelets	X		X			X	X[7]
PTT, PT/INR (if on anticoagulants)	X	*as clinically indicated*					
Creatinine, creatinine clearance bilirubin, AST[8], ALT[8], ALP, LDH, albumin, total protein, glucose, amylase[9], lipase[9]	X		X			X	X[7]
TSH[10]	X				X[11]		
Radiology							
Chest/abdomen CT scan. Brain CT scan or MRI. Other scans as necessary to document disease.	X (within 28 days prior to randomization or 35 if negative)			X[12]	X[12]	X[12]	X[12]
Adverse Events							
Adverse event assessment	X	Continuously				X	X[13]
Telephone contact			X[14]				
Other Investigations							
Dipstick Urinalysis (including protein, specific gravity, glucose and blood)	X						
MUGA[15]	X (within 28 days prior to randomization)						
Pregnancy Test[16]	X	*as clinically indicated*					
ECG	X	*as clinically indicated*					
Archival Tumour Tissues (must confirm at time of randomization that tissue is available for submission for PD-L1 testing)	X						
Correlative Studies							
Whole blood, serum and plasma	X[17]	X (cycle 4 only)	Once at time of PD[3]				
cfDNA	X[18]						

Table continues on next page…

Required Investigations	Pre-study (≤14 days prior to randomization)	Day 1 each cycle, and as clinically indicated	Days 1 & 8 cycle 1; then Day 1 subsequent cycles (unless clinically indicated)	6 weeks after baseline (during treatment)	Every 12 weeks after baseline (during treatment)	4 weeks after completion of protocol therapy[1]	Post-treatment[2]: Every 12 weeks until PD[3], then every 24 weeks until death
Quality of Life							
EORTC QLQ- C30+ QLQ-LC13 + trial specific checklist	X	X				X	X[19]
Economic Analysis							
Health Utilities Index (EQ-5D 5L)	X	X				X	X[19]
Resource Utilization Assessment		X				X	X[19]

1. Completion of therapy refers to the end of the last cycle (the cycle should be 21 or 28 days in duration depending on the regimen even if the off protocol therapy decision is made earlier in the 21 or 28-day period). For Arm 1 this refers to the durvalumab and tremelimumab only – post progression chemotherapy is not considered "on-treatment". For Arm 2 this includes durvalumab, tremelimumab, protocol chemotherapy and/or maintenance pemetrexed (investigator's choice treatment following progression is considered "off-treatment").
2. Patients who discontinue protocol therapy without iCPD and who do not receive second line therapy should be seen every 12 weeks from completion of therapy until progression. The first visit is therefore 8 weeks after the 4 week visit and then continues every 12 weeks thereafter. Patients who discontinue protocol therapy with iUPD and who begin second line therapy are to be followed q 24 weeks from the date of the 4 week post treatment visit. Patients who discontinue protocol therapy with iCPD are to be followed q24 weeks from the date of the 4 week post treatment visit.
3. Progressive disease as defined in Section 8.
4. To be done every 12 weeks until relapse or progression (iCPD) for patients with CR/iCR, PR/iPR, SD/iSD response as defined in Section 8. For patients with iUPD, confirmatory scans must be performed at least 4 weeks, but no longer than 8 weeks, after iUPD was identified.
5. Patients will be monitored before, during 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. A second 1-hour observation period is recommended after the first infusion of durvalumab. In 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 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. Standard chemotherapy (for patients on Arm 2) may be administered during the durvalumab observation period according to local practice.
6. Laboratory Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, 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 II for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.
7. Required at 4 week post treatment visit. To be done additionally every visit thereafter to follow abnormal lab results felt to be related to protocol therapy.
8. It is preferable that both AST and ALT are assessed. For sites where only 1 of these parameters is routinely measured first and the other assessed if the first is abnormal, then either AST or ALT would be acceptable.
9. It is preferable that both amylase and lipase tests are done. For sites where only one of these tests is routinely performed then either lipase or amylase is acceptable.
10. Free T3 and free T4 will be measured if TSH is abnormal.
11. On treatment prior to infusions every 12 weeks (for example, at weeks 12, 24, 36, 48 and so forth).
12. The first post-baseline scans should be done at week 6, then week 12, then every 12 weeks thereafter (EXCEPTION: Brain scans need only be repeated after baseline if there are brain lesions at baseline, if patient is symptomatic or if it is standard of care at the centre). To ensure comparability, the baseline scans and subsequent scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Maintain schedule of week 6, week 12 then every 12 weeks even if cycles are delayed. If iUPD occurs, confirmatory scans must be performed at least 4 weeks, but no longer than 8 weeks, after iUPD was identified.
13. To capture adverse events related to protocol therapy, including late events.
14. Telephone contact to assess adverse events required on day 8 of cycles 1 and 2. Note: if the patient is already in clinic to receive gemcitabine on day 8, the contact may be made in clinic but a Telephone Follow-Up Report should still be completed.
15. Only if significant cardiac history; and as clinically required. If a MUGA cannot be done, an ECHO may be substituted.
16. 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.
17. Must be taken after consent is obtained but prior to start of treatment.
18. For sites who perform the buffy coat and plasma separation for cfDNA analysis, the blood may be collected after consent but prior to treatment. For sites who send the STRECK tubes to CCTG for buffy coat and plasma separation, the blood must be collected after consent and after randomization but prior to treatment. Please refer to the Correlative Manual for full details.
19. Until progressive disease. Questionnaires to be completed at time of progressive disease if not done within 2 weeks prior.

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 minimal follow up form. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

6.0 RANDOMIZATION PROCEDURES

6.1 Entry Procedures

All randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and 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 BR.34 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing patients, please contact the help desk (link in EDC) or the BR.34 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG BR.34)
- patient's initials (may be coded)
- for CCTG sites; informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- for CCTG sites: tissue banking/optional consent version date and date signed by patient
- for non-CCTG sites: date informed consent and tissue banking consent signed by patient
- 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.

6.3 Stratification

Subjects will be stratified by:

- Squamous vs. non-squamous NSCLC
- IVA vs. IVB
- smoking status (< 100 cigarettes vs previous vs current)

6.4 Randomization

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 participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

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

7.0 TREATMENT PLAN

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

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

Patients will be randomized 1: 1 to one of two treatment arms. All patients will receive durvalumab and tremelimumab. Patients on Arm 1 will receive durvalumab (until progression) and tremelimumab (maximum of 4 doses). Patients randomized to Arm 2 will receive standard platinum combination chemotherapy plus durvalumab (until progression) and tremelimumab (maximum of 4 doses); maintenance pemetrexed (if applicable) continues until progressive disease. Note: Planned chemotherapy duration is 4 cycles.

Each treatment cycle is defined as either

- 21 days (during platinum combination chemotherapy). Chemotherapy AND durvalumab ± tremelimumab must be given on day 1 of each treatment cycle (if applicable); dosing cannot be split.
- 28 days (when durvalumab +/- tremelimumab given alone) OR during the maintenance phase for patients receiving pemetrexed + durvalumab (non-squamous histology).

7.1 Durvalumab and Tremelimumab Treatment Plan

7.1.1 *Drug Administration*

When durvalumab is given with tremelimumab, tremelimumab will be administered first. Durvalumab will start immediately after the tremelimumab infusion (during the post-tremelimumab observation period). Consult the Pharmacy Information Manual for complete details.

Arm 1: Durvalumab and Tremelimumab Alone

Agent(s)	Dose	Route	Duration	Schedule	Frequency
Durvalumab/	1500 mg	IV	60-120 min	Day 1 each cycle	Every 28 days for 4 cycles
Tremelimumab	75 mg				
FOLLOWED BY MAINTENANCE					
Durvalumab*	1500 mg	IV	60	Day 1 each cycle	Every 28 days until PD
* *Patients on maintenance therapy and with PD, who are clinically stable, who according to the judgment of the treating physician had clinical benefit while receiving tremelimumab in the induction phase and meet all eligibility criteria used at randomization, can receive one additional dose of tremelimumab.*					

Arm 2: Durvalumab and Tremelimumab in Combination with Chemotherapy

During Platinum Combination Therapy

When durvalumab is given with tremelimumab, tremelimumab will be administered first. Durvalumab 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.

Up to four cycles of platinum combination therapy should be administered q3 weekly, each with durvalumab and tremelimumab as shown below. If patients receive fewer than 4 cycles of platinum combination therapy, the remaining cycles of durvalumab/tremelimumab (to a total of 4) should be given after the completion of the platinum combination therapy (with maintenance pemetrexed if applicable).

During Platinum-Doublet Chemotherapy

Agent (s)	Dose	Route	Duration	Schedule	Frequency
Durvalumab	1500 mg/	IV	60-120 min	Day 1 of each cycle	Every 21 days x 4 cycles*
Tremelimumab	75 mg				
* *If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (to a total of 4) should be given after combination of platinum doublet chemotherapy – (with maintenance pemetrexed if applicable)*					

After Platinum Doublet Chemotherapy is "Completed":
(providing patient has not experienced severe immune related toxicity requiring durvalumab and tremelimumab discontinuation)

With and without Pemetrexed Maintenance Therapy

Agent(s)	Dose	Route	Duration	Schedule
Durvalumab*	1500 mg	IV	60 min	Every 4 weeks** until PD
* *Patients on maintenance therapy and with PD, who are clinically stable, who according to the judgment of the treating physician had clinical benefit while receiving tremelimumab in the induction phase and meet all eligibility criteria used at randomization, can receive one additional dose of tremelimumab.* ** *If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (to a total of 4) should be given with maintenance pemetrexed*				

7.1.2 *Premedication for Immunotherapy*

No routine premedication (e.g. for nausea) or prophylaxis for hypersensitivity is required. Management of symptoms should take place as necessary (see Section 7.1.5 below). Premedication is not expected to be required. See Section 7.1.5 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). Please see section 7.2.1 for premedication for chemotherapy.

7.1.3 *Patient Monitoring*

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

Drug administration	Infusion duration	Vital signs and Monitoring*	
Tremelimumab	60 min	**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	**First infusion:** 60 min observation period after administration of 1st cycle of durvalumab/tremelimumab **Subsequent infusions:** At Investigator's discretion (30 min recommended)
Durvalumab	60 min		
* *Guidelines for management of infusion-related reaction are summarized in 7.1.5 and Appendix II.*			

Tremelimumab infusion	Tremelimumab observation**	
	Durvalumab infusion*	Durvalumab observation**
<---------- 60 minutes ---------->	*<---------- 60 minutes ---------->*	*<---------- 60 minutes ---------->*
* *Durvalumab 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 (Arm 2 only).*		
** *The length of the observation period for subsequent infusions will be at the investigator's discretion (30 minutes is recommended)*		

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

All patients should be closely monitored according to guidelines in Section 5 and be advised to contact the treating centre in the case of significant toxicities.

7.1.4 *Dose Modifications*

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

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

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

The next cycle should not be given until the laboratory criteria in Section 4.1.8 are met and resolution of all drug related toxicity to ≤ grade 2. For patients who have discontinued all standard chemotherapy agents and are continuing on durvalumab +/- tremelimumab alone, criteria for creatinine clearance may be lower. Please contact CCTG to discuss if asymptomatic/not felt to be clinically significant.

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

For patients where a dose of tremelimumab is omitted from one or more of the first four cycles of therapy, 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.

7.1.5 *Management of Toxicity*

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

1. The CCTG senior investigator should be contacted if any serious or severe (grade 3 or 4) immune related toxicity occurs.
2. Treat each of the toxicities with maximum supportive care (including slowing / interrupting / omitting the agent suspected of causing the toxicity where required).
3. 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.
4. All dose modifications should be documented with clear reasoning and documentation of the approach taken.

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

- Patient evaluation to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
- Symptomatic and topical therapy should be considered for low-grade events.
- For persistent (greater than 2 to 3 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone PO 1-2 mg/kg/day or IV equivalent and contact CCTG Senior Investigator.

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 PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate

- More potent immunosuppressives (refer to individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids.
- Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient and be discussed with CCTG.

7.1.5.1 *Management of Infusion Reactions*

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

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

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

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

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

7.2 Chemotherapy Regimens (Arm 2)

Four cycles of platinum doublet therapy will be administered as indicated below. Chemotherapy is to start 15 minutes into the durvalumab observation period and monitoring of vitals will be per local standard practice.

Prior to randomization, the investigator must indicate whether the patients will receive cisplatin or carboplatin.

Note: patients who discontinue cisplatin or carboplatin and continue on pemetrexed alone are considered to have switched to pemetrexed maintenance even if fewer than 4 cycles of platinum doublet therapy have been administered.

7.2.1 *Premedication*

Patients should receive standard premedication according to the product monograph and local and provincial formulary guidelines including hydration (for cisplatin)

For patients receiving pemetrexed who have a creatinine clearance of 45 to 79 ml/min, NSAIDs should be held for 2-5 days prior and 2 days after pemetrexed (refer to pemetrexed product monograph).

In addition, pre-medication for pemetrexed should include:

- Vitamin B12 (1000 mcg IM every 9 weeks) and folic acid (0.41 mg PO daily) should be started ≥ 1 week prior to pemetrexed administration and continue throughout and 3 weeks after last dose of pemetrexed) or local equivalent
- Dexamethasone 4mg PO BID for 3 days starting day before chemotherapy suggested for rash prophylaxis or local equivalent.

IMPORTANT: All patients with non-squamous tumor histology (who would be scheduled to receive pemetrexed if randomized to Arm 2) should begin folic acid and vitamin B12 ≥ 1 week prior to randomization, in line with local practice. This is to ensure protocol treatment can begin within two working days of randomization.

The use of steroids for the prevention and treatment of emesis should be minimised where feasible and other effective anti-emetics used where possible. If emesis is well controlled, investigators should consider reducing or discontinuing steroids for subsequent cycles

The following are recommended as initial premedication.

Cisplatin	1. Aprepitant 125 mg po pre-chemotherapy on Day 1 then 80 mg po od on Days 2 – 3 *OR* Fosaprepitant 150 mg IV pre-chemotherapy on Day 1 AND 2. Granisetron 2 mg po or 1 mg IV pre-chemotherapy on Day 1 *OR* Ondansetron 8 mg po bid or 8 mg IV on Day 1 starting pre-chemotherapy *OR* Dolasetron 100 mg po pre-chemotherapy on Day 1 OR Palonosetron 0.25 mg IV pre-chemotherapy on Day 1 AND 3. Dexamethasone 10 mg IV pre-chemotherapy on Day 1
Carboplatin	1. Granisetron 2 mg po or 1 mg IV pre-chemotherapy on Day 1 *OR* Ondansetron 8 mg po bid or 8 mg IV on Day 1 starting pre-chemotherapy *OR* Dolasetron 100 mg po pre-chemotherapy on Day 1 *OR* Palonosetron 0.5 mg po or 0.25 mg IV pre-chemotherapy on Day 1 AND 2. Dexamethasone 4 mg po pre-chemotherapy on Day 1 OPTIONAL addition in cases of uncontrolled emesis despite above 3. Aprepitant 125 mg po pre-chemotherapy on Day 1 then 80 mg po od on Days 2 – 3 *OR* Fosaprepitant 150 mg IV pre-chemotherapy on Day 1
Inadequate control of emesis using above recommendations	Aprepitant/fosaprepitant as above Dexamethasone at standard doses

7.2.2 *Pemetrexed and Platinum Treatment Plan*

Combination therapy

Pemetrexed: 500 mg/m^2	Day 1	q 21 days x 4 cycles
Cisplatin: 75 mg/m^2 *	Day 1	
* carboplatin AUC 6 may be substituted but must be specified at randomization Total carboplatin dose (mg) will be calculated according to the Calvert formula: Carboplatin dose (mg) = (target AUC) x (GFR +25); GFR = glomerular filtration rate (see Section 4.1.8) The maximum dose based on a GFR estimate is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used. Please refer to the following link for more information: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm		

Maintenance

Pemetrexed: 500mg/m^2	Day 1	q 28 days until disease progression or unacceptable toxicity

7.2.3 *Gemcitabine and Platinum Treatment Plan*

Gemcitabine and Cisplatin

Gemcitabine: 1250 mg/m^2	D 1 and 8	q 21 days x 4 cycles
Cisplatin: 75 mg/m^2	D 1	

Gemcitabine and Carboplatin

Gemcitabine: 1000 mg/m^2	D 1 and 8	q 21 days x 4 cycles
Carboplatin AUC 5	D 1	

7.2.4 *Pemetrexed, Gemcitabine and Platinum Dose Modifications*

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

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. Please refer to the relevant Product Monographs. Centres may use written national / provincial/ local guidelines for dose adjustments.

Important: If Day 1 of a cycle is delayed due to AEs related to chemotherapy, the infusion of durvalumab +/- tremelimumab should also be delayed until the Day 1 treatment may be given. If the patient permanently discontinues treatment with chemotherapy he/she may continue to receive treatment with durvalumab +/- tremelimumab.

For arm 2 patients experiencing chemotherapy-related toxicities that require a delay in the start of the next scheduled cycle of > 21 days for unresolved adverse events, consideration should be given to discontinuation of further chemotherapy. Patients that are unable to tolerate chemotherapy may continue to receive immune therapy study agents.

If the start of the next treatment cycle is delayed by > 21 days due to an adverse event(s) that is deemed related to both chemotherapy and immunotherapy, the treating investigator should contact CCTG for approval before restarting chemotherapy and/or immunotherapy.

7.3 Duration of Therapy

Protocol treatment will continue until confirmed disease progression as defined in Section 8 or intolerable toxicity. However, four cycles of platinum doublet therapy will be given, and a maximum of 4 doses of tremelimumab.

7.4 Concomitant Therapy

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

7.4.1 *Permitted*

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

7.4.2 *Not Permitted*

- Use of cytokines.
- Administration of any other anti-cancer therapy is not permitted while the patient is receiving protocol therapy. Thereafter, patients may be treated at the investigator's discretion.
- Other investigational therapy.
- Concurrent radiation treatment; (Note: if patients require palliative radiation or prophylactic radiation (e.g. of brain) consult CCTG for exception to this rule; protocol therapy will need to be held prior to and during the radiation).
- Corticosteroids IV or PO (except for the treatment of ≥ grade 3 infusion reaction 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.
- Blood donation.
- Live attenuated vaccines should not be given through 30 days after the last dose of protocol treatment.
- EGFR inhibitors or other tyrosine kinase inhibitors are not allowed while on protocol treatment. Should be used with caution in the 90 days post last dose of durvalumab.

7.4.3 *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 this time, treatment with durvalumab +/- tremelimumab should be omitted and treatment with standard chemotherapy (Arm 2 only) should continue if, in the investigator's opinion, the patient is well enough. Per guidelines contained in Appendix II, durvalumab +/- tremelimumab may resume once event stabilizes to Grade ≤ 1 and the steroids have been tapered to ≤ 10 mg of prednisone per day (or equivalent).

Length of steroid tapering is usually dictated by the severity of the immune mediated adverse event. 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. Please refer to Section 7.1.5.

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

If symptoms recur or worsen during steroid tapering, increase the steroid dose until stabilization or improvement of symptoms, then resume steroid tapering at a slower rate. Inability to reduce steroid 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. Please contact CCTG to discuss further if desired.

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 2016]*.

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

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

8.2 RECIST 1.1 Response and Evaluation Endpoints

8.2.1 *Measurable Disease*

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

8.2.2 *Non-measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.3 *Target Lesions*

When more than one measurable tumour lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

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

8.2.4 *Non-target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

8.2.5 *Response*

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

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

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomised studies.

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

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

Table S1: Integration of target, non-target and new lesions into response assessment

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

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

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

8.3 iRECIST Response Assessment

Overall response will also be assessed using iRECIST *[Seymour 2016]*. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression (called pseudo-progression or PSPD).

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 S2: 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 S3: 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.

8.4 Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

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

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

8.5 Methods of Measurement

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

8.5.1 *Clinical Lesions*.

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

8.5.2 *Chest X-ray*

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

8.5.3 *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.[4] 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).

8.5.4 *Ultrasound*

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

8.5.5 *Endoscopy, Laparoscopy*

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

8.5.6 *Tumour Markers*

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

8.5.7 *Cytology, Histology*

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

9.0 SERIOUS ADVERSE EVENT REPORTING

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

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

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events, regardless of whether they are unexpected or related to protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported in an expedited manner. Any late serious adverse event occurring after this 30-day period which is related to protocol treatment must also be reported in an expedited manner (see Section 9.2 for reporting instructions).
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

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:

1. *Any immune related adverse event (irAE) requiring high dose steroids is by definition medically significant and must be reported as such.*
2. *If a patient shows an AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, refer to Appendix II for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.*

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 Data Management Guidebook for EDC Studies posted on the BR.34 section of the CCTG website (www.ctg.queensu.ca).

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

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

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

FAX paper SAE Report to: BR.34 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2411

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the BR.34 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

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

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of childbearing potential (WOCBP) and men who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criteria 4.1.11.

Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

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

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

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

9.3.2 *Pregnancy Reporting*

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

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

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

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

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

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

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

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada and Other Regulatory Authorities

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

The CCTG will provide expedited reports of SAEs to the Local Sponsor in other countries for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out) and they will report per local requirements.

9.5 CCTG Reporting Responsibility to AstraZeneca

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

9.6 CCTG and AstraZeneca Reporting Responsibilities

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

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 BR.34 web-based safety monitoring utility. For some participating countries, your Local Sponsor will provide full details of the process to be followed in your country (for example translated documents or submission to Central Ethics Boards).

For Canadian sites 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 and of any other events required by local regulations and policies.

The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial BR.34 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.

For all other sites, Safety Reports and Safety Updates will be provided to sites and local sponsors and must be reported per local rules and local sponsors will advise.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients should receive 4 cycles of platinum doublet therapy and no more than 4 doses of tremelimumab. All other protocol treatment should continue until one of the following is met:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Patients who are not clinically stable or who have confirmed disease progression (iCPD) as defined in section 8.0. Note: Patients who are clinically stable but meet the criteria for iUPD should continue on treatment until the next disease assessment at least 4 weeks later. It is recommended that the next imaging assessment be no longer than 8 weeks later in order to ensure patients remain fit for salvage therapies. Clinical stability is defined as:
  - stability or improvement in performance status
  - no clinically relevant increase in disease related symptoms such as pain or dyspnea (generally understood to mean a requirement for increased palliative intervention as below)
  - no requirement for increased management of disease related symptoms including increased analgesia, radiation or other palliative care.
- Request by the patient.
- Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Duration of Protocol Treatment

(see Section 8.0 for response definition)

Therapy will continue until disease progression unless the conditions described in Section 10.1 are met.

Patients on maintenance therapy shown to have PD may receive one additional dose of tremelimumab (75 mg) along with their next durvalumab infusion as long as ALL of the following criteria are met:

- Patient is clinically stable.
- According to the judgment of the treating physician, the patient had clinical benefit while receiving tremelimumab in the induction phase.
- ECOG performance status of 0 or 1.
- Laboratory values meet the criteria outlined in Section 4.1.8.

10.3 Therapy After Protocol Treatment is Stopped

Therapy after iCPD at the discretion of the investigator but it is expected that patients on Arm 1 will receive chemotherapy (platinum doublet or single agent per local guidelines). Details of subsequent anti-cancer treatment will be collected on the case report forms.

10.4 Follow-up Off Protocol Treatment

A patient is considered to be off protocol treatment after all protocol treatment agents have been discontinued.

All patients will be seen at 4 weeks after the end date of the final cycle of treatment.

Please note for patients who go off protocol treatment with iUPD, confirmatory scans should be performed at least 4 weeks, but no longer 8 weeks, after iUPD was documented.

Patients who discontinue protocol therapy without iCPD and who do not receive second line therapy should be seen every 12 weeks from completion of therapy until progression. The first visit is therefore 8 weeks after the 4 week visit and then continues every 12 weeks thereafter.

Patients who discontinue protocol therapy with iUPD and who begin second line therapy are to be followed q 24 weeks from the date of the 4 week post treatment visit.

Patients who discontinue protocol therapy with iCPD are to be followed q24 weeks from the date of the 4 week post treatment visit.

Final report (Form 6) is required for all patients at the time of death. See Appendix IV - Documentation for Study.

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Data Review

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

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

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

11.2 Central Radiology Review

Centralized collection of all radiology will be required for all randomized patients. Radiology review of a portion or all cases will be undertaken. Full details of imaging submission will be provided in the BR.34 Response Review Manual.

11.3 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

A detailed Correlative Manual will be provided on the BR.34 trial specific website, which will include details regarding sample preparation, handling and shipping.

12.1 Protocol-Mandated Correlative Studies

Archival Tumour Block/Cores/Slides:

Samples must be submitted after randomization. At the time of randomization sites must confirm that samples are available and will be submitted for PD-L1 assays as a mandatory part of the study.

The collection of a representative block/cores/slides of the diagnostic tumour tissue (from primary or metastatic tumour) is an important part of this trial. In order to do so, the tissue will be forwarded to the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario where they will be carefully stored. All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

Blocks are the preferred material to collect, as it is well known that tissue materials (including protein and nucleic acid integrity) on unstained sections deteriorate rapidly within 3-6 months after preparation. Submission of blocks 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. If a block cannot be submitted, a minimum of two 2 mm cores and a predetermined number of unstained sections must be submitted. Please refer to BR.34 Correlative Manual for further details.

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.

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

Planned Priority Assays on Tumour Tissue Include:

- PD-L1
- PD-1
- Evaluation of lymphocyte infiltration including subtypes by immunohistochemistry (TILs, CD3, CD4/CD8 and FOXP3 (or FOXP40))
- Genomic profiling including mutational burden

Blood Collection

The CCTG is interested in exploring the use of surrogate tissues such as blood, serum and plasma in evaluating potential prognostic or predictive biomarkers, or as evidence of pharmacodymanic effects. Blood samples will be collected on all patients.

Assays include:

- cfDNA

12.2 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/cores/slides will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

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 blood will take place and any proposals approved will have undergone ethics approval.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

This is a prospective, randomized, multi-center study in patients with metastatic squamous and non-squamous non-small cell lung cancer. The primary objective is to compare the effect between the treatments of durvalumab/tremelimumab and the durvalumab/tremelimumab + standard 1st line platinum-based chemotherapy on overall survival (OS) in the study population. Patients will be randomized at a 1:1 ratio to two study treatment arms, stratified by smoking status (< 100 cigarettes vs previous vs current), disease stage (IVA vs. IVB), and histology type (squamous vs. non-squamous).

Secondary objectives include comparisons of progression free survival (PFS), objective response rate (ORR), quality of life (QoL), health economics between treatment arms, assessment of the toxicity and safety of the study treatments, and to determine the prognostic and predictive effect of tumour PD-L1 expression assessed by IHC on efficacy.

13.2 Primary Endpoints and Analysis

Overall Survival

Overall survival (OS) is the primary endpoint of the study. It is defined as the time from randomization to the date of death due to 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 known alive date. All randomized patients will be included in the analysis of OS. A Kaplan-Meier estimate of proportions of patients alive in each treatment arm will be displayed. The 95% confidence intervals for the median OS will be computed using the method of Brookmeyer and Crowley. In the primary analysis, the two treatment arms will be compared using the log-rank test stratified by stratification factors at randomization. The effect of potential prognostic factors on survival will be assessed using Cox regression model. The Schoenfeld residual plots will be used to check the model assumption for the Cox regression.

Progression Free Survival

Progression free survival (PFS) is a secondary endpoint of this study, which is defined as the time from randomization to the date of the first documented disease progression (based on RECIST 1.1) or death due to any cause. A patient who stops treatment with study drug and goes on to receive alternative therapy for NSCLC, prior to documentation of disease progression, will be censored on the date alternative therapy began. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All randomized patients will be included in the analysis of PFS. All analyses for OS will be similarly performed for PFS.

Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with a documented complete response, partial response (CR + PR) based on iRECIST criteria. The primary estimate of ORR will be based on all patients randomized, and compared using Cochran- Mantel-Haeszel test stratified by stratification factors at randomization between the study new treatment and the standard control arms.

Safety Analysis

All patients who have received at least one dose of study 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 Version 4.0. A Fisher's exact test will be used to compare adverse events between the study new treatment and the standard control arms if required.

13.3 Sample Size and Duration of Study

The primary objective is to determine if the addition of standard 1st line chemotherapy to durvalumab and tremelimumab can prolong the OS in comparison to the durvalumab and tremelimumab alone. Assuming a 2-year survival rate of 40% for the durvalumab and tremelimumab arm, to detect a hazard ratio (HR) of 0.67 in comparison of chemotherapy + durvalumab and tremelimumab to durvalumab and tremelimumab with 80% power using a 1-sided 5% level test, we need to accrue 300 patients (150 in each arm) in 18 months, the required number of events (a minimum of 155) would be observed with another 15 months follow up. Log-rank test stratified by stratification factors at randomization will be used to test the difference in OS between 2 treatment arms.

13.4 Safety Monitoring

The standard dose and schedule for the durvalumab and tremelimumab combination is 1500 mg durvalumab +/- 75 mg tremelimumab q4 weekly. This is supported by efficacy and safety data from multiple tumour types. To align with the chemotherapy schedule in this study, we propose to use the standard durvalumab/tremelimumab doses at a q3 week interval. This dose schedule appears to be tolerable. Considering that 75mg of tremelimumab is the minimum dose from an efficacy point of view and in order to keep same ratio of durvalumab/tremelimumab, 1500 mg of durvalumab is proposed for this current study. The rationale for this is supported by the data from the CCTG IND.226 trial and trials sponsored by the pharmaceutical company which suggested that no change in adverse events was observed with increasing dose of durvalumab when combined with tremelimumab. Therefore, giving 1500 mg of durvalumab q 3 weekly will not pose significant risks to patient safety.

To better support the use of the 1500 mg durvalumab +/- 75 mg tremelimumab q3 weekly and to ensure safety and tolerability in this larger randomized study, the safety of the proposed dose and schedule will be tested and a step-wise approach will be adopted. An initial safety review will take place when the first 30 patients (15 each arm) have completed the 1st cycle of treatment and have had 21 days of follow-up. These 30 patients will continue to be followed for long-term safety. A second safety review will take place when an additional 30 patients (15 each arm) complete the 1st cycle of treatment and have had 21 days follow up, giving a total of 60 patients. At the time of this second review, it is expected that the initial 30 patients will have longer-term follow-up data that may extend into the maintenance period. This safety review will be carried out by DSMC in an unblinded fashion. The DSMC will make a recommendation on whether recruitment should continue or be held. The DSMC will continue to monitor the study conduct approximately every 6 months thereafter.

In addition, adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually to the DSMC and at investigators' meetings.

13.5 Interim Analysis

There will be a planned interim analysis on progression free survival (PFS). Assume a 26% 1 year PFS rate for patients on durvalumab and tremelimumab arm, and we would check if the addition of standard 1st line chemotherapy to durvalumab and tremelimumab can reduced the risk of disease progression by 30% (increase a 1-year PFS rate from 26% to 39%). The interim analysis will be performed when the accrual is finished with about 154 events (PDs or deaths), we would claim that the study treatment is unlikely to have the target effect if we observed a HR of greater than 0.86. Otherwise, we will continue the trial to obtain the required number of events for final analysis on OS. If the true HR is 0.7 or less, we will have a 90% chance to continue the trial for final analysis on OS. As the futility analysis will not inflate the type I error, the final analysis on OS will be based a 5% 1-sided test.

13.6 Quality of Life Analysis

The quality of life (QoL) of patients will be assessed using EORTC QLQ-C30 *[Aaronson 1993]* and the lung cancer module (QLQ-LC13) questionnaires plus additional study specific questions.

The EORTC QLQ-C30 is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100. The QLQ-LC13 lung cancer module *[Bergman 1994]* includes questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The validity and reliability have been studied by the EORTC Study Group on Quality of Life. The EORTC QLQ-C30 and module will be scored according to the EORTC QLQ-C30 Scoring Manual, and analyzed accordingly.

The QOL data will be analyzed to look for statistically and clinically significant differences between the study treatments versus the standard treatment groups. The standard CCTG QoL Response Analysis categorizing patients as either having improved, stable, or worsened QoL will be used *[Osoba 2005].* A change score of 10 points from baseline is defined a priori as clinically relevant. For functional scales and global health status, patients will be considered to have QoL improvement if reporting a score of 10-points or better than baseline at any time of QoL assessment. Conversely, patients will be considered worsened if reporting a decrease in score of 10-points or worse than baseline at any time of QoL assessment without above defined improvement. Patients whose scores fall between 10-point changes from baseline at every QoL assessment will be considered as stable. In contrast to functional scales, for the determination of patient's QoL response, classification of patients into improved and worsened categories will be reversed for symptom scales.

In comparing QoL between treatment arms, time points of particular interest are after cycle 4 (upon completion and near completion of induction chemotherapy), and at 6 and 12 months from the start of treatment.

An additional analysis of QoL at baseline and on treatment will be performed comparing individuals who achieve a tumour response with and without evidence of pseudoprogression.

13.7 Economic Analyses

The purpose of the CCTG economic evaluation is to determine the incremental cost-effectiveness and cost-utility of durvalumab and tremelimumab concurrently with combination chemotherapy from a government payer perspective, over a lifetime time horizon by prospectively collecting economic and resource utilization information during the clinical trial. The objectives are:

a) To determine an incremental cost effectiveness ratio reported as a cost per life-year (LY) gained for the combination of standard first-line chemotherapy and durvalumab and tremelimumab to durvalumab and tremelimumab alone. A cost-effectiveness analysis will be conducted. The mean overall cost per patient for each of the two study treatment arms will be calculated to determine the addition cost per life-year gained.

b) To determine an incremental cost utility ratio in cost per quality-adjusted life-year (QALY) gained of durvalumab and tremelimumab plus standard first-line chemotherapy vs. durvalumab and tremelimumab. A cost-utility analysis will be conducted. Preference weights for comparator arms will be determined through the US Valuation of the EuroQol EQ-5D Health States, with EQ 5D scores taken directly from the study database. Quality-adjusted survival in the two treatment arms will be generated by multiplying the utility value by the amount of time spent in that utility state. The mean incremental cost per QALY in the study will be calculated. *[S. Valuation of the EuroQol EQ-5D Health States, December 2005.]*

The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Major drivers of medical care costs, namely hospitalization, chemotherapy and survival, will be varied ± 20%, to examine the impact on the base-case incremental cost effectiveness ratios (ICERs). Bootstrapping and the development of a cost-effectiveness acceptability curve will also be conducted.

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and AstraZeneca, may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- 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 groups and investigators included: (a list of the groups and individuals who have contributed patients and their institutions)."

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair /s to write up the results of the study within a reasonable time of its completion. If after a period of six months following 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 participating institutions 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) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CCTG.

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

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

Obtaining Consent for Research on Children

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

15.4 Discontinuation of the Trial

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

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

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

15.5 Retention of Patient Records and Study Files

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

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

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

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

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

15.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).
Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

15.7 On-Site Monitoring/Auditing

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).

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

As this trial is conducted under a CTA with Health Canada and other Regulatory authorities, your site may be subject to an inspection.

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

16.0 REFERENCES

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APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

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

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

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

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

(MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 17Nov2020 Version

The Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion Related and Non Immune-Mediated Reactions can be downloaded at:
DoseMod-ToxicityMgmntGuidelines_17Nov2020.pdf

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution (Canada)
Durvalumab and tremelimumab will be supplied by AstraZeneca via the distributor to participating centres. Details will be provided at study activation.

All other agents are commercially available.

Drug Distribution (International)
Details will be provided by your monitor.

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

Initial Drug Supply
Details will be provided at study activation

Drug accountability and drug re-order forms will be available on the BR.34 trial website.

Drug Ordering (Re-supply)
Details will be provided at study activation.

Drug Accountability
The investigational products are to be prescribed only by the investigator and co-investigators on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained accounting for the receipt of the investigational product and for the disposition of the product (Drug Accountability Log, available on the BR.34 trial website).

Drug Destruction
Expired/used study drug may be destroyed as per local standard operating procedures. Destruction of expired/used drug must be documented on the Drug Accountability Log and a copy of the destruction certificate kept on file in the pharmacy and is subject to on site monitoring/audit. The CCTG Study Coordinator must be contacted prior to destruction of expired medication to ensure an extension of expiry date is not expected. Expired trial medication may be destroyed per local policy, AFTER accountability and reconciliation has been completed and documented by the site and confirmed with CCTG. 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 IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except Quality of Life/Health Economics Questionnaires will be completed on paper by the patient and the answers will be entered into the EDC system by centre staff. 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 BR.34 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		Within 2 weeks of randomization	Copies of signed consent form and tissue banking consent[2], relevant surgical pathology and radiology reports, tumour measurement sheet (TMS), PD-L1 testing results (if done)
Baseline Report		Within 2 weeks of randomization	
Correlative Studies Report (Tumour and Blood)		Within 2 weeks of randomization, updated within 4 weeks of collection of correlative bloods for cycle 4 and progression	Consent form[2]
Concomitant Medications Report	Continuous running-log folder		
Treatment Report (includes maintenance treatment)	Every 21 or 28 days	Within 2 weeks of end of cycle	Relevant radiology reports
Telephone Follow-Up Report[3]	AE assessment on day 8 of cycles 1 and 2	Within 2 weeks of the contact	
End of Treatment Report	End of treatment	Within 2 weeks of end of treatment	
4 Week Follow Up Report	4 weeks from end of last cycle	Within 2 weeks of 4 weeks visit	Relevant radiology reports, TMS
Follow Up Report	Every 12 weeks from end of treatment for patients that have not progressed	Within 4 weeks of visit	Relevant radiology reports, TMS
Relapse/Progression Report	Upon disease progression	Within 4 weeks of progression	Relevant radiology and pathology reports
Short Follow-up Report	After progression, every 24 weeks	Within 4 weeks of follow-up visit	
Death Report	When patient dies	Within 4 weeks of patient's death	Copy of autopsy report if performed
SAE Report[4]	At the time of event and reported to CCTG	Within 1 working day	

footnotes on next page …

1 Scan and upload in the EDC Supporting Document Upload Tool (SDUT) - please refer to the slide set on the BR.34 website for guidance. Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) as not submitted. All patient identifiers, other than the CCTG patient ID assigned at enrollment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements. Acceptable methods include:

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

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

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. Centres are expected to redact the participant's name and signature on the submitted copy, leaving only a portion visible (e.g. initials or loops) to confirm that a person has signed but that cannot identify that individual.

For all other centres: submission of consent forms is not required but they will be reviewed on site.

3 If patients are already in clinic to receive gemcitabine treatment on day 8 of cycles 1 and 2, the contact may be done in person, but a Telephone Follow-Up Report should still be completed.

4 See Section 9.0 Serious Adverse Event Reporting for details.

The collection of the following information will ***NOT*** be done through the EDC system. Instead submit as follows:

Data	Required at	Collection /Submission	Comments
Quality of Life Questionnaire	Prior to randomization On treatment: Day 1 of each cycle Each follow up visit until, and including, progression	Patient to complete on paper; site CRA to enter relevant data (as required) in the EDC system within corresponding folders	Retain questionnaires at the site
EQ-5D Questionnaire			

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. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, 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

If the study protocol involves cycle-based treatment, the quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (up to 3 days prior to treatment day 1 is acceptable). 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: **BR.34**

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

During Treatment (Durvalumab +/- tremelimumab +/ chemotherapy +/- maintenance pemetrexed):

☐ Day 1 cycle 2 ☐ Day 1 cycle 3 ☐ Day 1 cycle 4 ☐ Day 1 cycle 5 ☐ Day 1 cycle 6

☐ Day 1 cycle 7 ☐ Day 1 cycle 8 ☐ Day 1 cycle 9 ☐ Day 1 cycle _____

Off Treatment – (until progression):

☐ at time of progression (must be completed at PD, unless done within 2 weeks of PD)

☐ week 4

then ☐ wk 12 ☐ wk 24 ☐ wk 36 ☐ wk 48 ☐ wk 60 ☐ wk 72 ☐ wk 84 ☐ wk 96 ☐ wk _____

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.

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 (BR.34)

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 go on to the next page

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

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not At All	A Little	Quite a Bit	Very Much
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body? If yes, where_____	1	2	3	4
43. Did you take any medicine for pain? 1 No 2 Yes If yes, how much did it help?	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**
44. Did you have itchiness of the skin?	1	2	3	4
45. Did you have a skin rash?	1	2	3	4
46. Did you have blurring of vision?	1	2	3	4

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.

APPENDIX VII - HEALTH UTILITIES ASSESSMENT

Introduction

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, disease free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making
- They can be used as a weighting factor to adjust survival by quality of life
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses

Health utilities data can be used in a variety of ways:

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

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

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

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

- pre-randomization (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. Pre-treatment Assessment

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

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

3. Assessments During Treatment

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

4. Assessments During Follow-up

The health utilities 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 overall health 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. Four 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.

D. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic.

6. Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D assessment in the clinic, the questionnaire should be read to them and the answers recorded by 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.

Health Utilities Questionnaire – ENGLISH

CCTG Trial: **BR.34**

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 health utilities assessment: please check (✓)

☐ Prior to randomization

During Treatment (Durvalumab +/- tremelimumab +/- chemotherapy +/- maintenance pemetrexed):

☐ Day 1 cycle 2 ☐ Day 1 cycle 3 ☐ Day 1 cycle 4 ☐ Day 1 cycle 5 ☐ Day 1 cycle 6

☐ Day 1 cycle 7 ☐ Day 1 cycle 8 ☐ Day 1 cycle 9 ☐ Day 1 cycle _____

Off Treatment – (until progression):

☐ at time of progression (must be completed at PD, unless done within 2 weeks of PD)

☐ week 4

then ☐ wk 12 ☐ wk 24 ☐ wk 36 ☐ wk 48 ☐ wk 60 ☐ wk 72 ☐ wk 84 ☐ wk 96 ☐ wk _____

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.

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

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

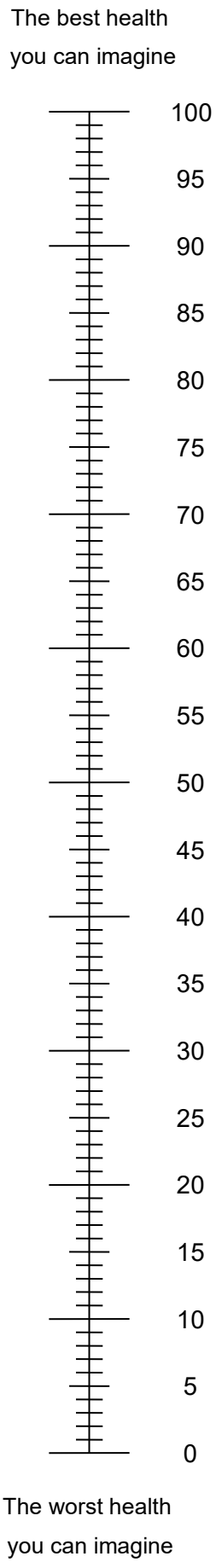
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX VIII - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 8th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

APPENDIX IX - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

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

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

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

Minor Protocol Deviations:

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

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

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.

Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
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)	Joel Lefebvre Study Coordinator, CCTG Email: jlefebvre@ctg.queensu.ca	613-533-6430	613-533-2941
	or: Dr. Francisco Vera-Badillo Senior Investigator, CCTG Email: fverabadillo@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Natasha Leighl Study Co-Chair Email: Natasha.Leighl@uhn.ca		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Francisco Vera-Badillo Senior Investigator, CCTG or: Joel Lefebvre Study Coordinator, CCTG	613-533-6430	613-533-2941
DRUG ORDERING See Appendix III for full details.	Refer to BR.34 Pharmacy Information Manual		
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		