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A PHASE III PROSPECTIVE DOUBLE BLIND PLACEBO CONTROLLED RANDOMIZED STUDY OF ADJUVANT MEDI4736 IN COMPLETELY RESECTED NON-SMALL CELL LUNG CANCER

A Lung Immunotherapy NSCLC Consortium (LINC) Trial of the CCTG, IFCT, CEEOG, NCI-Naples, NVALT, KCSG, ALTG and NHMRC CTC, GECP, WJOG

CCTG Protocol Number: **BR.31**
IFCT Protocol Number**: IFCT1401**

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(For Contact Information of Study Personnel see Final Page.)

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to CCTG and Astra Zeneca.

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

I will provide copies of the protocol and access to all information furnished by CCTG and Astra Zeneca 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 Astra Zeneca and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Astra Zeneca and CCTG of any such disclosure.

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

Any supplemental information that may be added to this document is also confidential and proprietary to Astra Zeneca and CCTG and must be kept in confidence in the same manner as the contents of this protocol. I will retain all furnished information in confidence, prevent its disclosure to third parties and will not use it, other than for the purposes of the study, during the study and for a period of seven years from the expiration or termination of the study. I acknowledge that this time period is longer than the five years generally required under the Participating Centre Agreement with CCTG and I will ensure that all study personnel receiving this information are informed of the obligations of confidentiality under this agreement and are made subject to these same obligations of confidentiality.

I acknowledge that a letter of indemnification from AstraZeneca may be obtained from CCTG upon request.

_____	_____	_____
Qualified Investigator Signature	Printed Name	Date

Protocol Number: CCTG BR.31/IFCT1401

CENTRE: _____

TREATMENT SCHEMA

This is a multi-centre, prospective, randomized, placebo-controlled trial of the human monoclonal antibody directed against programmed cell death ligand 1 (PD-L1) MEDI4736 in completely resected primary stage IB (≥ 4cm), II and IIIA non-small cell lung cancer patients.

Stratification:

- stage (IB (≥ 4cm), II, IIIA)
- pre-treatment PD-L1 expression (A [≥ 50%], B [25-49%] vs. C [1-24%] vs. D [< 1%])
- adjuvant platinum based chemotherapy (≥ 300 mg/m^2 cisplatin/equivalent* vs. < 300 mg/m^2 vs. no chemotherapy)
- accruing centre
- nodal sampling/dissection conducted in accordance with the European Society of Thoracic Surgeon (ESTS) guidelines (yes vs. no)

* *For patients receiving carboplatin regimens: [At least 3 cycles of carboplatin at AUC=6 or at least 4 cycles of carboplatin at AUC=5] vs. [less than 3 cycles of carboplatin at AUC=6 or less than 4 cycles of carboplatin at AUC=5] vs. [no chemotherapy].*

Completely resected Stage IB ≥ 4cm, II, IIIA NSCLC	**REGISTER**	Central lab determination of PD-L1 status	**RANDOMIZE*** →	**ARM A** MEDI4736** IV Day 1 every cycle*** →	Until 1 year from date of first treatment or earlier if disease relapse/new primary malignancy or unmanageable toxicity	End of treatment assessments (4 and 12 weeks from date of last infusion)	Follow up for disease event**** and survival (q 12 weekly until 2 years from randomization, then q 6 months in year 3 then annually until disease event, see Appendix XII). After disease event follow for survival (q 6 months until 3 years from randomization, then annually).
			→	**ARM B** Placebo** IV Day 1 every cycle*** →			

* Randomization will be **2:1** to the active treatment arm.
** 20 mg/kg q4w for 12 months (weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48).
*** 1 cycle = 4 weeks (28 days); see Section 8.1 for details.
**** Disease event is relapse, or any new invasive primary malignancy.

Planned Sample Size: 1360 patients

Endpoints

For all patients randomized to the trial, six patient sub-populations are defined according to the PD-L1 expression stratum as determined at randomization, and the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutation status determined retrospectively. The "EGFR-/ALK-" sub-population excludes only those with common activating EGFR mutations (defined as exon 21 L858R mutation or exon 19 deletions) or with ALK gene rearrangements (ALK+). The six study sub-populations are as follows:

- PD-L1 TC ≥ 25% and EGFR-/ALK-
- PD-L1 TC ≥ 1% and EGFR-/ALK-
- All EGFR-/ALK-
- All PD-L1 TC ≥ 25%
- All PD-L1 TC ≥ 1%
- All randomized patients

Primary Endpoint

- Disease free survival (DFS) for patients with NSCLC that is PD-L1 expression TC ≥ 25% and EGFR-/ALK-.

Secondary Endpoints

- DFS in the remaining 5 patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- Overall survival (OS) for patients in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- Lung cancer specific survival for patients in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- Adverse effects and tolerability of MEDI4736.
- Quality of life in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- Survival benefits participants judge necessary to make adjuvant immunotherapy worthwhile.
- Economic evaluation (cost effectiveness and cost utility).
- Evaluation of predictive/prognostic significance of PD-L1 expression.
- Evaluation of changes in plasma/serum cytokines and other blood and tissue based biomarkers after treatment with MEDI4736 and at disease event.
- Exploratory pharmacogenomic assays (baseline only).

1.0 OBJECTIVES

For all patients randomized to the trial, six patient sub-populations are defined according to the PD-L1 expression stratum as determined at randomization, and the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutation status determined retrospectively. The "EGFR-/ALK-" sub-population excludes only those with common activating EGFR mutations (defined as exon 21 L858R mutation or exon 19 deletions) or with ALK gene rearrangements (ALK+). The six study sub-populations are as follows:

- PD-L1 TC ≥ 25% and EGFR-/ALK-
- PD-L1 TC ≥ 1% and EGFR-/ALK-
- All EGFR-/ALK-
- All PD-L1 TC ≥ 25%
- All PD-L1 TC ≥ 1%
- All randomized patients

1.1 Primary Objective

To assess in comparison to placebo, the impact of adjuvant therapy with MEDI4736 given by intravenous infusion for one year on the disease free survival of patients with completely resected (stage IB ≥ 4cm, stage II or IIIA), non-small cell lung cancer that is PD-L1 expression TC ≥ 25%, and EGFR-/ALK-.

1.2 Secondary Objectives

- To compare the disease free survival in the MEDI4736 arm to the placebo arm in the remaining 5 patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To compare the overall survival in the MEDI4736 arm to the placebo arm in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To compare lung cancer specific survival in the MEDI4736 arm to the placebo arm in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To evaluate the nature, severity, and frequency of toxicities, between arms.
- To evaluate the quality of life between the two arms in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To determine the survival benefits participants judge necessary to make adjuvant immunotherapy worthwhile, and the factors influencing their preferences.
- To determine the incremental cost effectiveness and cost utility ratios for MEDI4736.
- To evaluate the prognostic and predictive significance of PD-L1 expression.
- To evaluate changes in plasma/serum cytokines and other blood and tissue based biomarkers after treatment with MEDI4736 and at the first disease event (relapse or new invasive primary malignancy).
- To explore polymorphisms that may be associated with outcomes.

2.0 BACKGROUND INFORMATION AND RATIONALE

Lung cancer is the second most common cancer in both men and women in North America *[Jemal 2007]*. Worldwide, 1.8 million cases of lung cancer are diagnosed annually *[Ferlay 2013]*. Non-small cell lung cancer (NSCLC) accounts for 80-85% of all pulmonary neoplasms *[Travis 2000]*. Although incidence and death rates have stabilized and are falling slowly, lung cancer is still the leading cause of cancer related-deaths worldwide, with an overall all-stage 5-year survival of approximately 17% *[DeSantis 2014]*. The primary treatment of early stage (I-IIIA) NSCLC is curative surgery. Currently only ~30% of patients present with stages I-IIIA lung cancer *[Datta 2003]*, however, with the advent of lung cancer screening this percentage is expected to increase *[The National Lung Screening Trial Research Trial 2011]*. Although patients treated with curative surgery have a better prognosis, the 5-year survival for patients treated with surgery alone remains low, ranging from 67% (stage IA) to 23% (stage IIIA) *[Mountain 1997]*.

The poor survival rates following surgical resection for patients with stage II and III disease have led several groups to investigate the utility of adjuvant chemotherapy in improving lung survival outcomes. Five large randomized trials have been undertaken to determine if adjuvant platinum-based chemotherapy after curative surgery for NSCLC confers a survival advantage: ALPI *[Scaggliotti 2003]*; IALT *[Arriagada 2004]*; JBR10 *[Winton 2005]*; CALGB 9633 *[Strauss 2008]*; and ANITA *[Douillard 2006]*. Three of these five trials showed statistically significant improvements in overall survival, ranging from 4% *[IALT]* to 15% *[JBR10]* at 5 years, corresponding to an absolute improvement in relapse-free survival from 49% to 61%. Of the two trials that did not demonstrate improved survival, one *[ALPI]* suffered from poor compliance to the treatment regimen (69%), and the second was a smaller trial (n=344) limited to patients with stage IB disease *[CALGB 9633]*, which was likely underpowered to detect a statistically significant improvement in overall survival. Interestingly, despite being limited to patients with stage IB disease, CALGB 9633 did demonstrate an overall survival hazard ratio comparable to the other adjuvant trials (HR=0.8) that included patients with more advanced disease, despite not achieving statistical significance *[Strauss 2008]*.

Since the publication of original adjuvant chemotherapy trials, a number of meta-analyses have confirmed the benefit of adjuvant platinum-based chemotherapy after surgical resection for NSCLC *[Pignon 2008; NSCLC Meta-analysis Collaborative Group 2010]*. In these meta-analyses, all-stage (IB-IIIa) hazard ratios were in the range of HR=0.86, corresponding to an absolute benefit of chemotherapy on overall survival of 4-5% at 5 years *[Pignon 2008, NSCLC Meta-analysis Collaborative Group 2010]*. The benefit of adjuvant chemotherapy, however, was demonstrated to be stage dependent (albeit using older staging criteria versions), with the benefit only reaching statistical significance for stages II and III *[Pignon 2008]*. While the role of adjuvant chemotherapy in stage I disease has historically been controversial *[Wakelee 2007]*, subgroup analyses in a number of trials in high-risk patients with stage IB disease (tumours $\geq$ 4cm) suggests that there may be an overall survival advantage with adjuvant chemotherapy in this subgroup of patients, comparable to those observed in stage II and III disease *[Strauss 2008]*. Neoadjuvant chemotherapy has also become accepted in some countries *[NSCLC Meta-analysis Collaborative Group 2014].*

Despite the established benefit of adjuvant chemotherapy after curative surgery for NSCLC, 30-60% of patients, depending on stage, will eventually relapse and die of their disease *[Hotta 2004]*. Furthermore, not all patients with early stage disease are eligible or willing to undergo chemotherapy following complete surgical resection *[Booth 2010]*. As such, the long-term prognosis of patients with NSCLC, even among those with early stage disease, remains poor. Novel therapies are, therefore, required to improve the clinical outcomes of completely resected NSCLC.

Based on their success in the advanced disease NSCLC setting *[Shepherd 2005],* molecularly targeted therapies have been evaluated in the adjuvant setting following complete surgical resection for NSCLC with limited success. Two large randomized trials have evaluated epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as adjuvant therapy in early stage resected NSCLC. The first was a phase III randomized controlled adjuvant study of 2 years of gefitinib versus placebo following surgical resection (stage IB-IIIA) *[Goss 2013]*. This study was terminated prematurely based on an unplanned analysis precipitated by the negative results of the ISEL trial in the advanced disease setting *[Thatcher 2005]*. Based on results of 503/1242 of the planned accrual, overall survival in this trial was not found to differ between treatment arms *[Goss 2013]*. Although limited by the premature closure of the trial, the results of this study suggest that in the adjuvant setting, gefitinib is unlikely to provide any meaningful benefit in an unselected population. Most recently, a second phase III randomized trial comparing two years of adjuvant erlotinib to placebo has also failed to demonstrate benefit of adjuvant EGFR-TKI therapy on prolonging disease-free survival, despite restricting enrolment to patients with high EGFR protein expression or increased EGFR gene copy number *[Kelly 2014]*. Despite the lack of success of earlier adjuvant trials targeting the EGFR pathway, the recent ADAURA study has shown that osimertinib treatment resulted in a statistically significant improvement in DFS, with an acceptable tolerability profile *[Wu 2020]*. In the context of early stage NSCLC, immunotherapeutic interventions that can both induce cell-mediated immunity against proliferating cancer cells following complete resection and establish immunologic memory that may guard against future recurrences through active immune surveillance is a particularly attractive therapeutic option.

Immune responses of the human immune system directly target tumours as part of the body's natural defence mechanisms. Cancers, however, can develop strategies that allow them to actively evade detection and immune-mediated apoptosis. The up-regulation of surface proteins, including programmed death-1 (PD-1), is one such strategy. Specifically, abnormal cell-surface expression of its ligand PD-L1 on tumours has been shown to induce T cell anergy, affording tumours protection against killer T-cell elimination *[Creelan 2014]*. Further, in the tumour microenvironment, PD-1 expressed on activated T cells has also been shown to limit T cell antitumour activity on cells reaching the tumour, when bound to its ligand, PD-L1 *[Fife 2008]*. Although, historically NSCLC has been considered to be non-immunogenic *[Holt 2011]*, emerging data suggests that lung cancers may actively evade attack by the immune system by expressing the PD-L1 ligand, allowing them to evade immune detection *[Topalian 2012; Dong 2002; Iwai 2002]*. PD-L1 overexpression has been noted in 40%-50% of NSCLC, across all stages and histologies *[Yang 2014; Konishi 2004; Mu 2011; Chen 2012]*. Although PD-L1 overexpression has in some studies been associated with negative prognostic factors, including higher-grade differentiation and vascular invasion *[Yang 2014]*, studies of PD-L1 expression and overall survival have been inconsistent *[Yang 2014; Konishi 2004; Mu 2011; Chen 2012]*. Targeting of PD-1 receptors and its ligands PD-L1 and inhibiting their engagement is an attractive therapeutic option in the early stage NSCLC, which may reactivate host immune responses and enable long-term tumour control. In preclinical studies, blocking the interaction between PD-1 and PD-L1 has been shown to induce immune responses in vitro *[Fife 2009]* and enhance antitumour T cell cytotoxic activity (MedImmune MEDI4736 Investigator Brochure edition 6.0). In a syngeneic tumour implantation model, PD-L1 inhibition has been shown to inhibit tumour growth in a T-cell dependent tumour manner *[Stewart 2011]*.

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, renal cell, colon and lung cancers *[Topalian 2012; Pardoll 2012; Brahmer 2012; Horn 2013; Grosso 2013; Garon 2013; Khleif 2013]*. In lung cancer, inhibition of the PD-1 checkpoint pathway by antibodies targeting either PD-1 or its ligand PD-L1 have yielded encouraging preliminary results, suggesting a "class effect" and validating this pathway as a therapeutic target in NSCLC. Phase I NSCLC cohorts of heavily pretreated patients have yielded dose-dependent objective responses ranging from 10%-32% *[Topalian 2012; Brahmer 2012; Horn 2013; Grosso 2013; Garon 2013; Khleif 2013]* with responses observed in patients with both squamous and non-squamous histologies. Notably, in such trials, the inhibition of the PD-1 checkpoint pathway with either anti PD-1 and anti-PD-L1 antibodies has been characterized by durable tumour responses or prolonged stable disease, often lasting longer than 6 months *[Topalian 2012; Brahmer 2012]*. Exploratory analyses of PD-L1 tumour expression and treatment response in these trials have confirmed the > 40% prevalence of PD-L1 expression in NSCLC, with some studies suggesting an association between treatment response and pre-treatment PD-L1 tumour expression *[Topalian 2012, Horn 2013, Garon 2013]*. However, the role of PD-L1 expression as a biomarker for clinical response to PD-1 pathway inhibition has yet to be validated. Immunotherapy with anti-PD-1 or anti-PD-L1 antibodies across many tumour types has been generally well tolerated, with common drug related adverse events mainly limited to grade 1 or 2 fatigue, diarrhea, rash, pruritus, nausea and decreased appetite. In clinical trials, grade 3 and 4 treatment-related adverse events have generally been reported in < 15% of patients *[Topalian 2012; Brahmer 2012]*. Observed immune-related adverse events thought to be the result of treatment are uncommon (< 2%), and include pneumonitis, vitiligo, colitis, hepatitis, hypophysitis and thyroiditis *[Topalian 2012; Brahmer 2012]*.

MEDI4736 is a novel IgG1-kappa PD-L1 inhibitor with potent and specific binding to PD-L1 at picomolar concentrations, which has directed mutations in the Fc region, limiting off-target cytotoxicity in PD-L1-expressing immune cells *[Khleif 2013; Stewart 2011]*. MEDI4736 has been shown to increase T-cell activation in vitro by blocking PD-L1/PD-1 engagement *[Khleif 2013]* and induces antitumour responses in tumour-bearing mice, with corresponding changes in peripheral immune markers *[Khleif 213]*. MEDI4736 has also been shown to inhibit tumour growth in vivo xenograft models *[Stewart 2011]*. A phase I expansion cohort of MEDI476 (10 mg/kg IV administered two weekly for one year) including 143 patients with advanced NSCLC demonstrated a disease control rate (response + stable disease ≥ 12 weeks) of 13% (39% in patients with PD-L1 positive NSCLC and 5% in patients with PD-L1 negative NSCLC). The safety profile was favourable with predominantly fatigue, pyrexia and gastrointestinal disturbance as the most common adverse effects, occurring in fewer than 15% of patients, and rare immune related events *[Segal 2014]*.

In advanced NSCLC, inhibition of the PD-1 immune checkpoint pathway has been shown to induce durable clinical responses across all histologies and is therefore of broad clinical relevance. MEDI4736 has a favorable safety profile and limited off-target T cell effects and has good pharmacokinetic and pharmacodynamic properties. Results of early trials with MEDI4736 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 PD-1 immune checkpoint pathway. MEDI4736 is particularly attractive as a therapeutic strategy in the adjuvant setting as it may generate immunologic memory and persistent activity in memory T cells, allowing for active and sustained surveillance and killing of tumour cells and possibly long term cure. NSCLC patients with PD-L1 expression positive resected tumours may be particularly sensitive to immunotherapy with MEDI4736 given accumulating evidence in patients with advanced disease. The study design and primary endpoints of this trial have been chosen to allow for the assessment of MEDI4736 efficacy in delaying disease relapse in patients whose tumours overexpress PD-L1 as well as all patients regardless of PD-L1 status. The primary analysis population has been selected based on the effectiveness of osimertinib for patients with resectable EGFR mutated (EGFRm) NSCLC *[Wu, 2020]* and corresponding meta-analyses that show limited effect of immune checkpoint inhibitors such as durvalumab in EGFRm or Anaplastic Lymphoma Kinase gene alteration (ALK+) NSCLC *[Khan, 2018; Wang, 2018].*

Assessment of Quality of Life (QoL) in all patients is an important aspect in this trial evaluating a new therapy when given to patients with NSCLC after surgical resection $\pm$ adjuvant chemotherapy. Any possible survival gains from new therapies need to be assessed in terms of their QoL impact. Patients on the placebo arm of the study may show improved QoL until, and if, NSCLC relapse / new primary malignancy occurs, whereas it is possible that patients on the MEDI4736 arm may have an initial decline in QoL over time, due to the effects of treatment. However, it is also possible that this can be counterbalanced if toxicity is mild or moderate by beneficial effects of the experimental agent. Thus, a patient perspective of the impact of treatment is felt to be an essential part of this study.

A well validated questionnaire in this patient population is needed, and cultural and linguistic adaptation is essential as this will be a multinational study with Canadian and international centres participating. The EORTC core QoL questionnaire (QLQ-C30) *[Aaronson 1993]* and lung cancer module (QLQ-LC13) *[Bergman 1994]* are commonly employed in lung cancer clinical trials, and satisfy these basic requirements *[Earle 2004]*. It will be possible to compare results of this study to QoL outcomes in other clinical trials performed by the Canadian Cancer Trials Group that also used the EORTC instruments. The EORTC QLQ-C30 and QLQ-LC13 include items that address the main side effects of MEDI4736. The Canadian Cancer Trials Group Quality of Life Item Bank was also searched for appropriate questions and additional questions will be appended to the EORTC instruments.

While targeted agents have shown benefits in multiple tumour sites including lung, colon and renal cell carcinoma, their adoption and governmental funding has been variable. For instance, bevacizumab has received notice of compliance from Health Canada for metastatic colon cancer yet provincial funding has been variable across the country due to an estimated cost-utility ratio of greater than $100,000 per quality adjusted life year gained. Therefore, accurate prospective economic data for any targeted agents are invaluable in assisting decision makers regarding funding issues. A prospective economic evaluation will be conducted in participating centres to determine the incremental cost-effectiveness and cost-utility of adjuvant MEDI4736 in 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, anxiety/depression) and each dimension comprises three levels (no problems, some/moderate problems, 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 14).

While MEDI4736 is a promising candidate for improving survival in completely resected NSCLC, any benefits will need to be considered against its inconvenience and adverse effects. A companion sub-study conducted in selected countries will determine the survival benefits participants judge necessary to make treatment with MEDI4736 worthwhile, and the factors influencing their preferences. The underlying goal of this sub-study is to improve multi-disciplinary communication, decision-making and care for future patients considering immunotherapy for NSCLC by revealing the judgments and attitudes of those who have been through this experience.

There is a significant history of correlative sciences research in CCTG lung cancer clinical trials. Analysis of molecular markers from the JBR.10 trial and as part of the LACE-Bio collaboration provided an important contribution to our understanding of prognostic and predictive variables for patients undergoing adjuvant therapy *[Zhu 2010; Friboulet 2013]*.

This trial will prospectively collect tissue and blood samples in all patients to further expand our knowledge of the predictive value of molecular variables. PD-L1 assays are integral to the stratification and selection of patients at randomization. Mutation profiling is critical in NSCLC and the relationship between known driver and other mutations and PD-L1 status as well as outcomes will be tested. A number of gene and molecular signatures have been reported which are hypothesized to allow more precise selection of patients for systemic therapy and these will be tested in an attempt to validate them. Immune markers such as lymphocyte infiltration will be explored. Other markers such as IFN-γ, tumour necrosis factor-α, IL-2, IL-6, IL-10, IL-8, and IL-12 may correlate with outcomes and response to therapy. If this proves to be the case, it may be feasible to better define a cohort of patients who are most suitable for therapy with agents such as MEDI4736. Genetic polymorphisms may play a role in both lung cancer risk and outcomes. Polymorphisms may predict differences in behaviour of the cancer, immune mechanisms, or cancer drug metabolism. In addition to these prospectively planned correlative studies, tissues will be banked for other testing that is likely to become relevant during the conduct of this study.

4.0 TRIAL DESIGN

This is a multi-centre, prospective, randomized, double blind, placebo-controlled trial of the human monoclonal antibody directed against programmed cell death ligand 1 (PD-L1) MEDI4736 in completely resected primary stage IB (≥ 4cm), II and IIIA non-small cell lung cancer patients.

4.1 Registration

Patients will be registered prior to submission of tumour blocks for PD-L1 estimation. (For China sites, patients will be registered prior to submission of tumour slides for PD-L1 estimation.)

4.2 Stratification

Patients will be stratified by:

- stage (IB (≥ 4cm), II, IIIA)
- pre-treatment PD-L1 expression (A [≥ 50%], B [25-49%] vs. C [1-24%] vs. D [<1%])
- adjuvant platinum based chemotherapy (≥ 300 mg/m^2 cisplatin/equivalent* vs. < 300 mg/m^2 vs. no chemotherapy)
- accruing centre
- nodal sampling/dissection conducted in accordance with the European Society of Thoracic Surgeon (ESTS) guidelines (yes vs. no)

* *For patients receiving carboplatin regimens: [At least 3 cycles of carboplatin at AUC=6 or at least 4 cycles carboplatin at AUC=5] vs. [less than 3 cycles of carboplatin at AUC=6 or less than 4 cycles of carboplatin at AUC=5] vs. [no chemotherapy].*

4.3 Randomization

Patients will be randomized (2:1) to receive MEDI4736 or placebo, to a planned sample size of 1360. Patients will not be selected for PD-L1 status.

5.0 STUDY POPULATION

This trial will study patients with completely resected primary stage IB (≥ 4cm in the longest diameter), II or IIIA non-small cell lung cancer (NSCLC). Staging will be according to the TNM staging system for lung cancer (7th edition). Note: Although T3N2M0 tumours have been reclassified to stage IIIB in the 8th edition of the IASLC staging system, these patients remain eligible (as stage IIIA under the 7th edition criteria).

5.1 Eligibility Criteria

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

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

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

5.1.1 Histologically confirmed diagnosis of primary non-small cell carcinoma of the lung according to WHO Classification of Tumours (WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. WHO/IARC Classification of Tumours, 4th Edition, Volume 7). Patients with large-cell neuroendocrine carcinomas are not eligible.

Patients must have an adequate histopathology (see Section 13), must consent to release of an adequate histological specimen for this protocol, and the tissue blocks must be available for submission after registration. Local policy must permit the submission of tissue blocks. It is the centres' responsibility to notify CCTG immediately of any changes in local policy that would preclude the submission of tissue blocks. If local policy requires this, blocks must have been stored in the Institutional Research Bank at the time of surgery to allow submission of blocks. Failure to provide tissue blocks for PD-L1 expression assessment will render the patient ineligible. Slides only will NOT be acceptable for PD-L1 expression assessment.

After registration but prior to randomization, tissue blocks from the surgically resected NSCLC must be submitted for PD-L1 assessment and the result must be available prior to randomization (see Sections 6 and 13). Patients will not be selected for PD-L1 status. (For China sites, patients will be registered prior to submission of tumour slides for PD-L1 estimation.)

Note: Patients with synchronous primary tumours will not be eligible due to the potential uncertainty regarding their appropriate PD-L1 status.

5.1.2 Patients must be classified post-operatively as Stage IB (≥ 4cm in the longest diameter), II or IIIA on the basis of pathologic criteria.

5.1.3 *Surgery and Previous Therapy for NSCLC*

Surgery:

- A pre-surgical PET scan of the thorax and a MRI or CT scan of the brain is considered standard of care and thus must be done prior to surgery. Patients in whom this was not done prior to surgery may still be enrolled providing that appropriate imaging is performed prior to randomization (see Section 6).
- Complete surgical resection of the primary NSCLC is also mandatory. All gross disease must have been removed at the end of surgery. All surgical margins of resection must be negative for tumour. Resection may be accomplished by open or VATS techniques.
- Lymph node mapping is defined by The International Association for the Study of Lung Cancer (IASLC) lymph node map. The nodal tissue should be labelled according to the recommendations of the American Thoracic Society. Surgeons are strongly encouraged to dissect or sample all accessible nodal levels in accordance with the European Society of Thoracic Surgeons guidelines. Accordingly, it is recommended that a minimum of 3 (three) lobe specific mediastinal nodal stations (N2), one of which should include station 7, and at least one N1 station - inclusive of the ones removed with the pulmonary specimen have been sampled at the end of the procedure.
- If preoperative CT and/or PET are suspicious for mediastinal nodal involvement, it is recommended that invasive mediastinal staging with mediastinoscopy or EBUS-TBNA be performed. Station 5 or 6 lymph nodes may be accessed by anterior mediastinotomy or VATS. This may also occur at the time of the surgical resection. If invasive staging shows disease in regional lymph nodes, they must be surgically removed. It is recommended that complete mediastinal lymph node dissection be undertaken for stage IIIA tumours.
- Surgery may consist of lobectomy, sleeve resection, bilobectomy or pneumonectomy as determined by the attending surgeon based on the intraoperative findings. Patients who have had only segmentectomies or wedge resections are not eligible for this study. Note: Where a resection has been extended by means of a wedge resection of an adjacent lobe in order to ensure complete resection of a tumour at or crossing a fissure between lobes, as long as the margins are clear this is acceptable. Where the resection of a second tumour nodule, even where not considered to be a co-primary, is undertaken by means of a wedge resection of a separate lobe then the patient is not eligible.

Prior Systemic Therapy:

- Pre-operative (neo-adjuvant) platinum based or other chemotherapy is not permissible.
- Patients may have received prior post-operative platinum based chemotherapy as per standard of care. Patients who discontinue chemotherapy for toxicity prior to completion of all planned chemotherapy are eligible.
- If adjuvant platinum based chemotherapy is given, it is strongly recommended that this be started within 8 weeks of surgery.
- Patients must have recovered from all acute, reversible toxic effects from chemotherapy (excluding alopecia).

- Patients who have not received adjuvant chemotherapy, and meet all other eligibility criteria, may be eligible under the following circumstances:
  - All patients who are eligible for adjuvant chemotherapy MUST be offered adjuvant chemotherapy prior to any discussion about this trial and that must be documented.
  - The patient has declined adjuvant chemotherapy, and in the opinion of the investigator, this is the patient's final decision after receiving appropriate information and adequate time to make the decision.
  - If in the view of the investigator, adjuvant chemotherapy is contraindicated due to an underlying intercurrent illness/ laboratory abnormality, which is not considered reversible within a reasonable timeframe for the patient to be eligible for adjuvant therapy, which must be documented.
- No prior anticancer therapy for treatment of NSCLC other than standard post-operative adjuvant chemotherapy is permissible.

Radiation:

- Patients with N2 disease only who receive adjuvant post-operative radiation therapy are eligible provided they meet the protocol specified timing criteria for surgery, adjuvant chemotherapy and randomization. Pre-operative radiation therapy is not permissible.

Timing between surgery and adjuvant chemotherapy and randomization:

Surgery:
- A minimum of 3 weeks must have elapsed between NSCLC surgery and randomization. A minimum of 4 weeks must have elapsed for other types of surgery. Complete post-operative wound healing must have occurred following any surgery.
- No more than 10 weeks may have elapsed between surgery and randomization for patients who have not received adjuvant chemotherapy.

For patients after adjuvant chemotherapy:
- For patients who received post-operative adjuvant platinum-based chemotherapy, a minimum of 2 weeks must have elapsed (but no more than 10 weeks) from the last administered dose of chemotherapy to the date of randomization.

For patients after post-operative adjuvant radiation therapy:
- For patients who received post-operative adjuvant radiation therapy, the patient must meet the protocol specified timing criteria for surgery, adjuvant chemotherapy and randomization. The post-operative radiation therapy must be completed prior to randomization.

5.1.4 The patient must have an ECOG performance status of 0, 1.

5.1.5 Hematology (done within 14 days prior to randomization and with values within the ranges specified below): If anemic, patients should be asymptomatic and should not be decompensated. Transfusions are permissible.

Absolute neutrophil count	$\geq$ 1.5 x 10^9/L or $\geq$ 1,500/μl
Platelets	$\geq$ 100 x 10^9/L or $\geq$ 100,000/μl

5.1.6 Biochemistry (done within 14 days prior to randomization and with values within the ranges specified below):

Total bilirubin*	≤ institutional upper limit of normal
Alkaline phosphatase	≤ 2.5 x institutional upper limit of normal
AST(SGOT) and ALT(SGPT)	≤ 2.5 x institutional upper limit of normal
Creatinine Clearance	≥ 40 ml/min

** excluding Gilbert's syndrome*

Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft Formula:

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

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

5.1.7 Other investigations detailed in Section 6 must have been performed within the timelines indicated.

5.1.8 Patient able (i.e. sufficiently fluent) and willing to complete the quality of life, economics and other questionnaires. The baseline assessment must already have been completed within required timelines prior to randomization. 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.

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

5.1.10 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

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

5.1.12 Age of at least 18 years.

5.2 Ineligibility Criteria

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

5.2.1 Patients with a history of other malignancies, except:

- adequately treated non-melanoma skin cancer,
- curatively treated in-situ cancer, or
- other malignancies curatively treated with no evidence of disease for ≥ 5 years following the end of treatment and which, in the opinion of the treating physician, do not have a substantial risk of recurrence of the prior malignancy.

5.2.2 A combination of small cell and non-small cell lung cancer, pulmonary carcinoid tumour or large-cell neuroendocrine carcinoma (LCNEC).

5.2.3 History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. NOTE: patients with Grave's disease and/or psoriasis not requiring systemic therapy within the last two years from randomization and patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement are not excluded.

5.2.4 History of primary immunodeficiency, history of allogenic organ transplant, 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.

** 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.*

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

5.2.6 History of hypersensitivity to MEDI4736 or any excipient.

5.2.7 Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects). Patients with a significant cardiac history, even if controlled, must have a LVEF > 50% within 12 weeks prior to randomization.

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

5.2.9 Patients with active or uncontrolled infections or with serious illnesses or medical conditions which would not permit the patient to be managed according to the protocol. This includes but is not limited to:

- known clinical diagnosis of tuberculosis;
- known active hepatitis B infection (positive HBV surface antigen (HBsAg)). Patients with a past or resolved hepatitis B infection (defined as presence of hepatitis B core antibody (anti-HBc) and absence of HBSAg) are eligible;
- known active hepatitis C infection. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA;
- known human immunodeficiency virus infection (positive HIV antibodies);
- known pneumonitis or pulmonary fibrosis with clinically significant impairment of pulmonary function.

5.2.10 Pregnant or lactating women. Women of childbearing potential must have a urine pregnancy test proven negative within 14 days prior to randomization. Men and women of child-bearing potential must agree to use adequate contraception as described in Section 11.3.1.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	• history including cigarette smoking • physical examination including height, weight, pulse, blood pressure • performance status • concomitant medications	Within 14 days of randomization
Hematology	• CBC including hemoglobin, differential, platelet count	Within 14 days of randomization
Biochemistry	• AST (SGOT) and ALT (SGPT)[15] • alkaline phosphatase • bilirubin • albumin • creatinine clearance • CRP • TSH [1] • INR/APTT • random glucose or fasting glucose • amylase[13] • lipase[13]	Within 14 days of randomization
Radiology	• baseline CT chest and upper abdomen (must include adrenal glands) [2]	Within 28 days of randomization[3]
	• MRI or CT of brain must be performed if not done prior to surgery • PET scan of thorax if not done prior to surgery	Prior to randomization[4]
	• other baseline imaging (e.g. bone scan, brain scan)	Required, within 28 days of randomization, only if suspicious signs/symptoms are present
Correlatives	• tumour tissue for assessment of PD-L1 status (archival tumour and normal tissue blocks)[12]	Tissue blocks from resected NSCLC must be submitted after registration and a minimum of 4 weeks prior to randomization (shorter timelines may be feasible but MUST be discussed with CCTG in advance (see Section 13 and Patient Enrollment and Tissue Submission Manual). (For China sites, slides of tumour tissue will be submitted in place of blocks for PD-L1 estimation.)
	• Whole blood, serum, plasma for correlatives[12]	Prior to Cycle 1, day 1 dosing [5]
Other Investigations	• ECG[14] • urinalysis • lung function tests: FEV1, FVC, TLCO[6] and SaO2 or SpO2 on room air [7] • pregnancy test if applicable • EGFR and ALK status (record only if already performed)	Within 14 days of randomization
	• LVEF [8]	Within 12 weeks prior to randomization
Adverse Event [9]	Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	Within 14 days of randomization
Quality of Life	EORTC QLQ- C30+ QLQ-LC13 + trial specific checklist	Within 14 days of randomization

table continues on next page …

Economics [10]	Health Utilities Index (EQ-5D)	Within 14 days of randomization
Patient Reported Outcome Sub-study [11]	Preferences for adjuvant immunotherapy	Within 14 days of randomization

1 If TSH is abnormal, both T3 and T4 should be measured (both are recommended but at least one of T3 or T4 is mandatory if TSH is abnormal).

2 Must be contrast enhanced CT scan, low dose surveillance CT is not acceptable. To ensure comparability, the baseline scans and subsequent scans to assess relapse 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). CT appearance consistent with post-operative change is expected and does not preclude randomization.

3 CT scan required prior to 28 days, however up to 42 days prior to randomization will be accepted.

4 To be completed prior to randomization. May be done before or after surgery or during chemotherapy.

5 Whole blood, serum and plasma for correlatives must be taken after consent is obtained but prior to day 1 dosing of cycle 1 – may be done after randomization providing it is done prior to day 1 dosing or within 14 days prior to randomization.

6 TLCO (transfer factor of the lung for carbon monoxide) is the same as DLCO (total diffusing capacity for the lung) but should NOT be confused with the abbreviation "TLC" (Total Lung Capacity).

7 Strongly recommended. Sites may opt out after discussion with CCTG but is mandatory for sites who have not opted out.

8 MUGA or ECHO, only for patients with significant cardiac history.

9 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

10 Canada, Australia/New Zealand, Netherlands, France, Japan, Italy, Bulgaria, Romania and China only. Other countries as identified.

11 Australia/New Zealand and Canada only. Other countries as identified.

12 Blood, and fluid and tissue samples collection for correlatives studies other than PD-L1 estimation will *not* be conducted in China sites.

13 Amylase not required if local standard of care is to omit amylase if lipase is normal. Lipase not required if local standard of care is to omit lipase if amylase is normal.

14 ECG only required if clinically indicated.

15 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.

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All registrations/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.31/IFCT1401 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients please contact the help desk (link in EDC) or the BR.31 Study Coordinator.

Registration

All consenting patients who are believed to be eligible (based on stage and performance status) will be registered using the EDC system prior to the submission of tissue blocks for PD-L1 estimation. An abbreviated eligibility check will be performed and a serial number assigned which must be used to identify the patient on the tissue blocks sent for PD-L1 testing prior to randomization.

Randomization

Randomization will be provided electronically. Patients are not selected for PD-L1 status of their NSCLC tumour and may be randomized after CCTG has received the results of PD-L1 testing. After the patient has been randomized successfully, the tissue blocks (normal and tumour) will be forwarded to the appropriate tissue repository. For patients that fail to be randomized, the tissue blocks will be returned to the site. (For China sites, patients will be registered prior to submission of tumour slides for PD-L1 estimation. For patients that fail to be randomized, submitted slides will not be returned to the site, but will be destroyed.)

The serial number assigned at registration must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG BR.31/IFCT1401)
- investigator CCTG user ID
- patient's initials (may be coded)
- for all centres – date informed consent and tissue banking consent signed by patient
- for CCTG centres - informed consent & tissue banking consent version dates, name of person conducting consent discussion and date signed.
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- height and weight
- stratification factors

7.2 Stratification

Patients will be stratified by:

- stage (IB (≥ 4cm), II, IIIA)
- pre-treatment PD-L1 expression (A [≥ 50%], B [25-49%] vs. C [1-24%] vs. D [<1%])
- adjuvant platinum based chemotherapy (≥ 300 mg/m^2 cisplatin/equivalent* vs. < 300 mg/m^2 vs. no chemotherapy)
- accruing centre
- nodal sampling/dissection conducted in accordance with the European Society of Thoracic Surgeon (ESTS) guidelines (yes vs. no)

* *For patients receiving carboplatin regimens: [At least 3 cycles of carboplatin at AUC=6 or at least 4 cycles carboplatin at AUC=5] vs. [less than 3 cycles of carboplatin at AUC=6 or less than 4 cycles of carboplatin at AUC=5] vs. [no chemotherapy].*

7.3 Randomization

Randomization will be provided electronically.

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

Note: The validity of results of the trial depends on the authenticity of the data and the follow up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

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

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

8.0 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 randomization.

8.1 MEDI4736/Placebo Treatment Plan

8.1.1 *Drug Administration*

Agent(s)	Route	Duration	Dose and Schedule**
MEDI4736 or matched placebo	IV	60 minutes*	**20mg/kg*** ** on weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48

* See Section 8.1.5.1 and Appendix XIII for duration in the case of an infusion reaction.

** From randomization to one calendar year taken from the date of the first infusion. No further infusions after one calendar year from the date of the first infusion even if all infusions described in protocol have not been received.

*** Four week minimum interval between infusions must be maintained; if infusion cannot be administered it should be omitted until the next planned infusion. In the event an infusion must be rescheduled (for example due to holidays, inclement weather, etc.) a window of +/- 3 calendar days is acceptable. For periods greater than 3 calendar days contact CCTG in advance for approval.

Do not administer MEDI4736/placebo unless treatment day tests meet the following criteria:

Absolute neutrophil count	$\geq 1.0 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Liver function tests	$\leq$ grade 1 or as per Appendix XIII

See Appendix XIII for additional details.

Blinding / Unblinding

Blinding is critical to the integrity of this clinical drug trial. If there is a need to break the blind this must be discussed with the CCTG as per Appendix IX.

8.1.2 *Premedication*

Premedication is not expected to be required. See Section 8.1.5.1 and Appendix XIII with respect to premedication of patients that have had a prior ≤ Grade 2 infusion-related reaction.

8.1.3 *Patient Monitoring*

Patients will be monitored during the infusion and for a 30 minute observation period after the infusion with assessment of vital signs as per local procedures (example of acceptable patient vital sign monitoring plan below). Guidelines for management of infusion-related reaction are summarized in Appendix XIII.

Drug administration	Infusion duration	Vital signs and Monitoring	
MEDI4736	60 min	Vital signs ≤ 30 minutes prior to start of infusion then every 30 ±5 minutes during infusion and observation periods	30 min observation period after administration of MEDI4736/

All patients should be closely monitored according to guidelines in Section 9.0 and be advised to contact the treating centre in the case of significant toxicities.

8.1.4 *Dose Adjustments*

The major toxic effects of MEDI4736 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 MEDI4736 leading to T-cell activation and proliferation. Potential immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with MEDI4736 and 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, cholangitis sclerosing, cystitis, uveitis and other events involving the eye (e.g. keratitis and optic neuritis), skin (e.g. scleroderma, vitiligo and pemphigoid), hematological (e.g. hemolytic anemia, immune-mediated neutropenia and immune thrombocytopenic purpura) and rheumatological (e.g. polymyalgia rheumatic and autoimmune arthritis) events, vasculitis, non infectious encephalitis or non infectious meningitis, and psoriasis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs. Please refer to the most recent version of the Investigator Brochure for incidence.

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

For the q 4 weekly schedule, if the infusion cannot be administered, it should be omitted until the next planned infusion. In the event an infusion must be rescheduled (for example due to holidays, inclement weather, etc.) a window of +/- 3 calendar days is acceptable. For periods greater than 3 calendar days contact CCTG in advance for approval. NOTE: if lab criteria are not met they can be re-tested and if criteria are then met infusion can be administered if within +/- 3 calendar days of planned infusion.

8.1.5 *Management of Toxicity*

Please refer to detailed toxicity management guidelines in Appendix XIII.

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

8.1.5.1 *Management of Infusion Reactions*

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

8.1.5.2 *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 XIII.

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.

8.1.5.3 *Hematologic Adverse Events*

See Section 8.1.1 for treatment day counts required for study agent administration.

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

8.1.6 *Duration of Therapy*

In the absence of disease relapse or new invasive primary malignancy as defined in Section 10 or intolerable toxicity, treatment with MEDI4736 /placebo will continue for 1 calendar year taken from date of first infusion irrespective of treatment omissions.

8.1.7 *Patient Compliance*

Trained medical personnel will administer MEDI4736/placebo. Treatment compliance will be monitored by drug accountability, as well as recording MEDI4736/placebo administration in the patient's medical record and case report form (CRF).

8.2 Concomitant Therapy

8.2.1 *Permitted*

- Concomitant medications or treatments (e.g. acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 8.2.2.
- Use of immunosuppressive medications for the management of acute immune related adverse events as outlined in Appendix XIII is acceptable. In addition, 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.

8.2.2 *Not Permitted*

- The chronic use of immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor alpha blockers.
- Live attenuated vaccines within 30 days of dosing with study agent. Inactivated viruses such as those in the influenza vaccine are permitted.
- Concurrent administration with other anti-cancer therapy, radiation therapy or investigational treatment.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

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

9.1 Evaluation During Protocol Treatment

Investigations		Timing	
History and Physical Exam[14] including:	• history including smoking history • physical examination including pulse, blood pressure • performance status • concomitant medications	Prior to each infusion until off protocol therapy.	
Hematology[1]	• CBC including hemoglobin, differential, platelet count	Prior to each infusion until off protocol therapy.	
Biochemistry[1]	• AST (SGOT) and ALT (SGPT)[15] • alkaline phosphatase • bilirubin • albumin • creatinine • random glucose or fasting glucose • amylase[13] • lipase[13]	Prior to each infusion until off protocol therapy.	
	• TSH [2]	Prior to infusions at week 4, 12, 24, 36, and 48 [3]	
	• INR/APTT	As clinically indicated.	
Radiology[4]	• CT scan chest and upper abdomen [5]	Every 12 weeks from randomization (CT schedule must be maintained regardless of treatment schedule)	
Other Investigations	• ECG • urinalysis • pregnancy test if applicable	As clinically indicated.	Romania only: ECG and Urinalysis as clinically indicated. High sensitivity urine pregnancy test on a monthly basis.
	• lung function tests: FEV1, FVC, TLCO[6] and SaO2 or SpO2 on room air	Only if pulmonary symptoms/suspicion of pneumonitis (see Section 8).	
Correlatives	• whole blood, serum, plasma[10]	At the time of discontinuation of MEDI4736/placebo	
	• serum for PK and ADA testing[11]	Prior to each infusion[12] at week 0, 4 and 24	
Adverse Events[7]	Patients must be evaluated after each cycle for adverse events		
Quality of Life	• EORTC QLQ- C30+ QLQ-LC13 + trial specific checklist.	Week 4, 12, 24, 36, 48 [8]	
Economics[9]	• EQ-5D	Week 4, 12, 24, 36, 48 [8]	
	• Resource Utilization Assessment	All cycles	

footnotes are on next page ...

1 **Bloodwork** Timing: Bloodwork done prior to randomization does not need to be repeated prior to first treatment. After the first treatment, 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 XIII 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.

2 If TSH is abnormal, both T3 and T4 should be measured (both are recommended but at least one of T3 or T4 is mandatory if TSH is abnormal).

3 TSH may be done up to 7 days prior to infusion.

4 Radiology assessments must be kept to calendar schedule irrespective of any dose omissions or delays in a treatment cycle. Scans can be done +/- 7 days from the date they are due without prior approval, HOWEVER, the due date for each disease assessment must be calculated based on the time from randomization, not the date of the previous assessment. If the schedule cannot be kept all attempts must be made to undertake the required imaging as soon as possible then patient must be put back on original imaging schedule.

5 Must be contrast enhanced CT scan, low dose surveillance CT is not acceptable. To ensure comparability, the baseline scans and subsequent scans to assess relapse 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). When relapse is first documented at any site, complete restaging is required to identify all sites of relapse (see Section 10.2).

6 TLCO (transfer factor of the lung for carbon monoxide) is the same as DLCO (total diffusing capacity for the lung) but should NOT be confused with the abbreviation "TLC" (Total Lung Capacity).

7 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

8 On day of planned infusion (up to 3 days prior to treatment is acceptable without prior approval) even if infusion is omitted.

9 Canada, Australia/New Zealand, Netherlands, France, Japan, Italy, Bulgaria, Romania and China only. Other countries as identified.

10 Blood and fluid samples collection (correlatives) will *not* be conducted in China sites.

11 Only for countries participating in pharmacokinetic and anti-drug antibodies sampling

12 For pre-dose, collection should be ≤ 1 hour before start of infusion, except for Week 0, which can be collected up to 14 days prior to randomization. NOTE: If the Week 0 sample is collected in conjunction with other baseline correlative samples it MUST still be labelled appropriately as Week 0 PK/ADA sample. If pre-treatment assessment bloodwork is collected more than 1 hour prior to the infusion, separate collection of PK/ADA samples is required within the specified timeline. If the infusion is omitted PK/ADA samples must still be collected. If it's known in advance that an infusion will be omitted the PK/ADA samples may be collected at the same time as the pre-treatment bloodwork collection. See Pharmacokinetic and Anti-Drug Antibodies Sampling Manual.

13 Amylase not required if local standard of care is to omit amylase if lipase is normal. Lipase not required if local standard of care is to omit lipase if amylase is normal.

14 History and Physical Exam Timing: History and Physical Exam done prior to randomization does not need to be repeated prior to first treatment. After the first treatment, pre-treatment history and physical exam 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).

15 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.

9.2 Evaluation After Protocol Treatment but Prior to Disease Relapse/New Invasive Primary Malignancy

The following investigations are to be performed for the period after discontinuation of MEDI4736/placebo (after completion of one year of therapy or for reasons other than a disease event (relapsed disease/new invasive primary malignancy as defined in Section 10.5)) until death. Follow-up visits after the 2-year post-randomization visit can be performed virtually if desired. CT scans must still be performed according to the protocol schedule if a follow-up visit is performed virtually.

All patients must be seen at 4 weeks after the date of last omitted or administered infusion (end of treatment visit). All patients must also be seen at 12 weeks after the date of last omitted or administered infusion. Follow up visits then occur every 12 weeks for 2 years from randomization, then at 30 and 36 months from randomization and then annually thereafter. See Appendix XII.

Investigations		Timing	
History and Physical Exam including:	• history • smoking history • physical examination including pulse, blood pressure[17] • performance status • concomitant medications[15]	Every follow up visit	
Hematology	• CBC including hemoglobin, differential, platelet count	Only at end of treatment visit (4 weeks after date of last infusion). Thereafter as clinically indicated only or to follow MEDI4736/placebo related AEs until resolution to grade 0-1.	
Biochemistry	• AST (SGOT) and ALT (SGPT)[16] • alkaline phosphatase • bilirubin • albumin • creatinine • random glucose or fasting glucose • amylase[13] • lipase[13]	Only at end of treatment visit (4 weeks after date of last infusion). Thereafter as clinically indicated only or to follow MEDI4736/placebo related AEs until resolution to grade 0-1.	
	• TSH[1]	At end of treatment visit (4 weeks after date of last infusion) and 12 weeks after date of last infusion (not subsequent q 12 weekly visits) then as clinically indicated, or to follow MEDI4736/ placebo related AEs until resolution to grade 0-1.[2]	
	• INR/APTT	As clinically indicated.	
Radiology[3]	• CT scan chest and upper abdomen [4] • other imaging as clinically indicated if suspicion of relapse or new primary invasive malignancy [5]	12 weekly for a total of 2 years from randomization, then at 30 and 36 months and then annually until final DFS analyses performed. See Appendix XII. Thereafter should be done according to local policy.	
Other Investigations	• ECG • urinalysis • pregnancy test if applicable	As clinically indicated.	Romania only: ECG and Urinalysis as clinically indicated. High sensitivity urine pregnancy test as per follow up visits.
	• lung function tests: FEV1, FVC, TLCO[6] and SaO2 or SpO2 on room air	Only if pulmonary symptoms or suspicion of pneumonitis (see Section 8.1.5.3 for full recommendations).	

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Investigations		Timing
Correlatives	• whole blood, serum, plasma	At the time of disease event or within 4 weeks of disease event.
	• serum for PK and ADA testing[12]	Only at 90 days post last received dose.[14]
Adverse Events[7]		Patients must be evaluated for MEDI4736/placebo related adverse events at each visit, including late events.
Quality of Life	• EORTC QLQ- C30+ QLQ-LC13 + trial specific checklist.	To be completed at 12 weeks from the date of last infusion, then each 12 weekly visit until 2 years from randomization.
Economics[8]	• EQ-5D	To be completed at each 12 weeks from the date of last infusion, then 12 weekly visit until 2 years from randomization.
	• Resource Utilization Assessment	Every follow up period.
Patient reported outcome substudy[9]	• Preferences for adjuvant immunotherapy	Only at 12 weeks post treatment visit.[10]

1 If TSH is abnormal, both T3 and T4 should be measured (both are recommended but at least one of T3 or T4 is mandatory if TSH is abnormal).

2 TSH may be completed within 7 days prior to visit.

3 **Radiology assessments must be kept to calendar schedule irrespective of any changes in treatment that occurred and irrespective of their off treatment date**. Scans can be done +/- 7 days from the date they are due without prior approval, HOWEVER, the due date for each disease assessment must be calculated based on the time from randomization, not the date of the previous assessment. If the schedule cannot be kept all attempts must be made to undertake the required imaging as soon as possible, then patient must be put back on original imaging schedule.

4 Must be contrast enhanced CT scan, low dose surveillance CT is not acceptable. To ensure comparability, the baseline scans and subsequent scans to assess relapse 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).

5 When relapse is first documented at any site, complete restaging is required to identify all sites of relapse (see Section 10.2).

6 TLCO (transfer factor of the lung for carbon monoxide) is the same as DLCO (total diffusing capacity for the lung) but should NOT be confused with the abbreviation "TLC" (Total Lung Capacity).

7 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

8 Canada, Australia/New Zealand, Netherlands, France, Japan, Italy , Bulgaria, Romania and China only. Other countries as identified.

9 Australia/New Zealand and Canada only Other countries as identified.

10 Preferences for adjuvant immunotherapy questionnaire should be completed at the 12 week post treatment visit. However, if missed, complete as soon as possible thereafter and enter in the next case report form.

11 Blood and fluid samples collection (correlatives) will *not* be conducted in China sites.

12 Only for countries participating in pharmacokinetic and anti-drug antibodies sampling

13 Amylase not required if local standard of care is to omit amylase if lipase is normal. Lipase not required if local standard of care is to omit lipase if amylase is normal.

14 At 90 days post last received dose, the blood collection can be +/- 7 days from the date they are required to accommodate visit schedule. In some cases, by the time the patient permanently stops protocol therapy, it may have been more than 90 days since their last administered infusion; however, the PK/ADA samples must still be collected. This should be done as soon as possible.

15 Required at end of treatment visit (4 weeks after date of last infusion) and 12 weeks after date of last infusion (not subsequent q 12 weekly visits)

16 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.

17 Physical exam is not required for visits performed virtually after the 2-year post-randomization visit.

9.3 Evaluation After Disease Relapse or New Invasive Primary Malignancy (During or After Protocol Treatment)

Should a patient relapse or develop a new invasive primary malignancy (as defined in Section 10.5) during the trial, details should be entered in the EDC disease event form and patient follow-up will be altered. All study patients must have a visit 4 weeks after the date of last omitted or administered infusion (end of treatment visit). All patients must also be seen at 12 weeks after the date of last omitted or administered infusion. If disease event occurs while on treatment, patients will be seen 4 and 12 weeks after the date of last infusion and will then be followed 6 monthly until 3 years after randomization, and then annually until death. After the 12-week follow-up visit, subsequent visits may be performed virtually.

Patients who have a disease event after MEDI4736/placebo is discontinued and the 4 and 12 week follow up visits have been completed will be followed 6 monthly until 3 years after randomization and then annually until death. The 6-monthly and annual visits may be performed virtually.

Treatments received by the patient after relapse and for new primary malignancies will be left to the discretion of the patient and his/her physician, but all treatments will be recorded in the EDC case report forms. All sites of NSCLC relapse or new primary malignancies will be recorded on the case report forms.

Investigations		Timing
History and Physical Exam including:	• history including smoking history, subsequent anti-cancer therapy • physical examination including pulse, blood pressure[16] • performance status • concomitant medications[14]	Every follow up visit.
Hematology	• CBC including hemoglobin, differential, platelet count	Only at end of treatment visit (4 weeks after the date of last infusion). Thereafter as clinically indicated only or to follow MEDI4736/placebo related AEs until resolution to grade 0-1.
Biochemistry	• AST (SGOT) and ALT (SGPT)[15] • alkaline phosphatase • bilirubin • albumin • creatinine • random glucose or fasting glucose • amylase[12] • lipase[12]	Only at end of treatment visit (4 weeks after date of last infusion). Thereafter as clinically indicated only or to follow MEDI4736/placebo related AEs until resolution to grade 0-1.
	• TSH[1]	Only at end of treatment visit (4 weeks after date of last infusion) and 12 weeks after the date of last infusion (not subsequent visits).[2] Thereafter as clinically indicated only or to follow MEDI4736/placebo related AEs until resolution to grade 0-1.
	• INR/APTT	As clinically indicated.
Radiology		As clinically indicated to follow toxicity to resolution (e.g. pneumonitis).

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Investigations		Timing	
Other Investigations	• ECG • urinalysis • pregnancy test if applicable	As clinically indicated.	Romania only: ECG and Urinalysis as clinically indicated. High sensitivity urine pregnancy test as per follow up visits.
	• Lung function tests: FEV1, FVC, TLCO[3] and SaO2 or SpO2 at room atmosphere	Repeat if pulmonary symptoms/suspicion of pneumonitis.	
Correlatives	• Whole blood, serum, plasma[10]	At the time of disease relapse/new primary malignancy or within 4 weeks of disease relapse/new primary malignancy if relapse/new primary malignancy occurs after off protocol treatment. [4]	
	• serum for PK and ADA testing[11]	Only at 90 days post last received dose.[13]	
Adverse Events[5]	Patients must be evaluated for MEDI4736/placebo related adverse events at each visit, including late events.		
Economics[6]	• EQ-5D	At time of relapse/new primary malignancy. [7]	
	• Resource Utilization Assessment	At time of relapse/new primary malignancy. [7]	
Patient Reported Outcome Sub-study[8]	• Preferences for adjuvant immunotherapy	Only at 12 weeks post treatment visit.[9]	

1 If TSH is abnormal, both T3 and T4 should be measured (both are recommended but at least one of T3 or T4 is mandatory if TSH is abnormal).

2 TSH may be completed within 7 days prior to scheduled visit.

3 TLCO (transfer factor of the lung for carbon monoxide) is the same as DLCO (total diffusing capacity for the lung) but should NOT be confused with the abbreviation "TLC" (Total Lung Capacity).

4 If relapse/new invasive primary malignancy occurs during treatment, correlatives only required at time of off treatment.

5 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

6 Canada, Australia/New Zealand, Netherlands, France, Japan, Italy, Bulgaria, Romania and China only. Other countries as identified.

7 To be completed at nearest visit following definitive relapse/new primary malignancy.

8 Australia/New Zealand and Canada only. Other countries as identified.

9 Preferences for adjuvant immunotherapy questionnaire should be completed at the 12 week post treatment visit. However, if missed, complete as soon as possible thereafter and enter in the next case report form.

10 Blood and fluid samples collection (correlatives) will *not* be conducted in China sites.

11 Only for countries participating in pharmacokinetic and anti-drug antibodies sampling.

12 Amylase not required if local standard of care is to omit amylase if lipase is normal. Lipase not required if local standard of care is to omit lipase if amylase is normal.

13 At 90 days post last received dose, the blood collection can be +/- 7 days from the date they are required to accommodate visit schedule. In some cases, by the time the patient permanently stops protocol therapy, it may have been more than 90 days since their last administered infusion; however, the PK/ADA samples must still be collected. This should be done as soon as possible.

14 Required at end of treatment visit (4 weeks after date of last infusion) and 12 weeks after date of last infusion (not subsequent q 12 weekly visits).

15 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.

16 Physical exam is not required for 6-monthly and annual visits performed virtually after confirmation of disease event.

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with MEDI4736/placebo.

10.1.2 Disease-free Survival. As disease-free survival is the primary endpoint in this study, it is vital that it be adequately and precisely documented. Disease-free survival shall be measured from the day of randomization until any of the following events: day of documented equivocal or definite relapse (local, regional or distant), diagnosis of a new primary invasive cancer (except squamous cell carcinoma and basal cell carcinoma of skin and any in situ cancer, completely excised and presumed cured), or death from any cause.

NOTE: Patients with Equivocal Changes should be re-imaged at the next planned time or earlier if clinically indicated. If relapse/new primary malignancy is confirmed the date of event is taken from the date that equivocal changes were first described.

Relapse will be categorized as local/regional or distant (see Sections 10.1.3 and 10.1.4).

10.1.3 Local or Regional Relapse. Local or regional relapse is defined as relapse in the area of the tumour bed, hilum or mediastinal lymph nodes.

10.1.4 Distant Relapse. Distant relapse is defined as spread of disease beyond the area of the tumour bed, hilum or mediastinal lymph nodes.

10.1.5 Overall Survival. Overall survival is defined as the time from randomization to the time of death (from any cause) or to the date the patient was last known to be alive.

10.1.6 Lung Cancer Specific Survival. Lung cancer specific survival is defined as the time from randomization to the date of death due to lung cancer.

10.2 Evidence of Disease Relapse

When relapse is first documented at any site, complete restaging is required to identify all sites of relapse.

10.2.1 *Local or Regional Relapse*

1. Definite - positive cytology, aspiration, or biopsy

   NOTE: In cases where there are single or multiple enlarging nodes in the mediastinum which are increasing in size over time as demonstrated by radiology (other than PET), a biopsy is not required but is preferred.

   NOTE: For instances where there is a single enlarged node that has not demonstrated sequential growth over time, the node must be biopsied to demonstrate definitive evidence of relapse.

   NOTE: Single timepoint evidence of hyperactivity on PET alone is not sufficient evidence of definite relapse. Serial increase in size must be concomitantly demonstrated.

2. Suspicious - radiological changes suggesting relapse

10.2.2 *Distant Relapse*

This is documented only when definite evidence is available but may be dated retrospectively to first onset of a suspicious sign as defined below.

A) Bone Marrow
   1. Definite - positive cytology, aspiration or biopsy.
   2. Suspicious - leukoerythroblastic blood picture (a bone marrow aspirate should be performed).

B) Skeletal
   1. Definite (one of 1a or 1b or 1c or 1d)
      a) X-ray evidence of lytic, blastic, or mixed lytic-blastic lesions on skeletal films with or without bone scan confirmation.
      b) CT / MRI evidence of skeletal metastases in a location where there was no lesion at baseline.
      c) Biopsy proof of bone metastases.
      d) Progressive bone scan or PET changes over at least a four week period showing development of new lesions is necessary in asymptomatic patients with only bone scan abnormalities.

NOTE: It is recommended PET or bone scan imaging be used to confirm findings from other imaging modalities.

NOTE: In the absence of progressive disease by scan a biopsy is recommended. Any positive bone scan in joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion of treatment failure.

C) Ascites and Pleural Effusions
   1. Definite - positive cytology.
   2. Suspicious - roentgenographic or clinical evidence.

D) Liver
   1. Definite (one of 1a or 1b)
      a) An abnormal liver ultrasound, CT, or MRI scan demonstrating solid space occupying lesions with or without nodular or non-nodular liver enlargement on physical examination. PET imaging can be used to confirm findings from other imaging modalities.

         NOTE: For lesions which are very small and the etiology is uncertain, these scans must be repeated to demonstrate growth in order to be considered definitive evidence of liver recurrence.

      b) Liver biopsy confirmation of metastatic disease.

NOTE: If the liver scan, ultrasound, CT or MRI scan findings are not definitive a liver biopsy is recommended.

E) Central Nervous System
   1. Definite (one of 1a or 1b)
      a) Positive CT scan, MRI scan or PET scan, usually in a patient with neurological symptoms.
      b) Meningeal involvement as documented by gadolinium MRI, biopsy or cytology.

F) Lung (example, ipsilateral or contralateral pulmonary nodules), excluding tumour bed, hilum or mediastinal lymph nodes. PET imaging can be used to confirm findings from other imaging modalities.

1. Definite (one of 1a or 1b)
   a) Biopsy or cytology proven disease.
   b) New lesions present on chest x-ray, CT, or MRI scan that are strongly suggestive of metastatic cancer, that cannot be attributed to other disease, and that cannot reasonably be confirmed by biopsy or cytology.

NOTE: In cases where there is a single enlarging lesion which is increasing in size over time as demonstrated by radiology (other than PET), a biopsy is not required but is preferred.

NOTE: For instances where there is a single enlarged lesion that has not demonstrated sequential growth over time, the lesion must be biopsied to demonstrate definitive evidence of relapse.

NOTE: Single timepoint evidence of hyperactivity on PET alone is not sufficient evidence of definite relapse. Serial increase in size must be concomitantly demonstrated.

2. Suspicious
   a) New lesions present on chest x-ray, CT, or MRI scan that are suggestive of metastatic cancer, that are unlikely to be attributable to other disease, and that cannot reasonably be confirmed by biopsy or cytology.

G) For Areas Not Specified Above

1. Definite (one of 1a or 1b)
   a) Biopsy or cytology proven disease.
   b) New lesions present on clinical examination, ultrasound, CT, or MRI scan that are strongly suggestive of metastatic cancer, that cannot be attributed to other disease, and that cannot reasonably be confirmed by biopsy or cytology. PET imaging can be used to confirm findings from other imaging modalities.

   NOTE: For adrenal lesions which are equivocal by other imaging methods, confirmation with MRI or angio-CT with adrenal protocol is required.

2. Suspicious
   a) New lesions present on clinical examination, ultrasound, CT, or MRI scan that are suggestive of metastatic cancer, that are unlikely to be attributable to other disease, and that cannot reasonably be confirmed by biopsy or cytology.

10.3 Dating of First Relapse

This should always be based on the first onset of a sign but never on the onset of a symptom. The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumour involvement is subsequently established. The diagnosis of recurrent disease by radiographs or scans should be dated from the date of the first positive record, even if this is determined in retrospect

10.4 Management Following Relapse

Patient management following local, regional or distant relapse is at the discretion of the investigator, but pertinent details need to be documented (see Section 9.3).

10.5 New Primary Malignancy

Should be pathologically confirmed and recorded in the case report forms.

Subjects developing any new invasive primary malignancies, except for adequately treated superficial squamous or basal cell carcinoma of the skin or any in situ cancer will discontinue protocol treatment (the exceptions based on the assumption that disease has been completely surgically excised and presumed cured, refer to Section 12.1).

Patient management following new primary malignancy is at the discretion of the investigator, but all treatments need to be documented (see Section 9.3).

11.0 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/facilities 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.

11.1 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 11.2 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 XIII for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.*

Note: Adverse events which are unequivocally related to the underlying malignancy or disease progression are NOT reportable Serious Adverse Events. These include such adverse events as admission for pain control, palliative care or paracentesis of malignant effusions. However, all deaths within 30 days of the last dose of protocol therapy must be reported as a Serious Adverse Event.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the BR.31 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.31 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

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

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

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the BR.31 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).

11.3 Other Protocol Reportable Events – Pregnancy/Exposure Reporting

In accordance with CCTG's inclusivity in research policy, women of childbearing potential (WOCBP) may be enrolled in this clinical trial. WOCBP are defined as women who have had a menstrual period during the last year and have not had a hysterectomy. Precautions are required to be taken to prevent pregnancy during the clinical trial when the research population includes WOCBP. This includes pregnancy testing, use of effective methods of birth control, and pregnancy as an exclusion factor. The trial sample informed consent form includes the potential for unidentified risks to the embryo/fetus. It also includes general information on pregnancy prevention and the required minimum period during which birth control must be utilized.

11.3.1 *Pregnancy Prevention*

WOCBP and males who are enrolled in the trial must be informed of the requirement to use one highly effective form of contraception or two effective forms of contraception. Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

A highly effective method of birth control is defined as those which result in a failure rate of < 1% per year when used consistently and correctly.

11.3.2 *Pregnancy Occurring in WOCBP Exposed to Study Agent*

Any female participant who becomes pregnant during the course of the trial should be instructed to stop taking study medication immediately.

The investigator should provide counselling and discuss the risks and possible side effects to the embryo/fetus from MEDI4736. Monitoring must continue until conclusion of the pregnancy. The same must occur for female partners of a male participant, or any female exposed to MEDI4736 when appropriate and compliant with local policy.

11.3.3 *Pregnancy/Exposure Reporting*

The investigator is required to report to the sponsor any pregnancy where the embryo/fetus could have been exposed to MEDI4736. This means pregnancies occurring in female participants, female partners of male participants, or females exposed through direct contact with the agent during their pregnancy (for example, environmental exposure involving direct contact with the agent). Pregnancies occurring up to 90 days after the completion of MEDI4736 must also be reported.

The investigator is required to inform CCTG within 24 hours of learning of the pregnancy using the SAE reporting form appropriate for the trial as indicated above. In the Adverse Event column please enter the following: “pregnancy, puerperium and perinatal conditions – other, specify” (fetal exposure). Please note that the CCTG patient identification number must correspond to the participant in the main trial. Specifically, in the case of pregnancy in the female partner of a male participant, the male participant’s patient identification number should be used for reporting purposes.

The SAE form must be updated to reflect the outcome of the pregnancy. For example:

- “pregnancy, puerperium and perinatal conditions – other, specify” (normal live birth),
- “pregnancy, puerperium and perinatal conditions – other, specify” (therapeutic abortion), or
- another term under "pregnancy, puerperium and perinatal conditions" as applicable.

Information on the medical history of the parents that may relate to assessing any potential fetal outcomes is requested, *as is information on the health of the newborn*. The narrative section of the SAE form should be used to communicate all relevant information pertaining to the pregnancy.

In cases where informed consent has not yet been obtained and cannot be obtained within 24 hours, the investigator is expected to report the pregnancy within this timeframe and subsequently amend the SAE form to provide the remaining information once consent has been obtained.

11.3.4 *Exposure During Lactation Reporting*

In addition, the investigator is required to report to the sponsor any incidence of exposure during lactation, if an infant or child may have been exposed through breast milk to MEDI4736 during breastfeeding by a female taking MEDI4736.

The investigator is required to inform CCTG within 24 hours of learning of the exposure using the SAE reporting form appropriate for the trial as indicated above. In the Adverse Event column please enter the following: "pregnancy, puerperium and perinatal conditions – other, specify" (infant exposure through lactation). Please note that the CCTG patient identification number must correspond to the participant in the main trial.

The SAE form must be updated to reflect the outcome of the exposure, if any. Appropriate follow-up is required to determine the occurrence and outcome of any adverse event in the infant.

In cases where informed consent has not yet been obtained and cannot be obtained within 24 hours, the investigator is expected to report the exposure within this timeframe and subsequently amend the SAE form to provide the remaining information once consent has been obtained.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

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

11.5 CCTG Responsibility for Reporting Serious Adverse Events to Other Health Authorities

The CCTG will provide expedited reports of SAEs 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) to the Regulatory Office contact of each Participating Group acting as sponsor in their country.

11.6 CCTG Reporting Responsibility to AstraZeneca

AstraZeneca will be notified of all received reportable serious adverse events (Section 11.1) within one working day of receipt by CCTG.

11.7 AstraZenecaReporting Responsibilities

AstraZeneca will notify CCTG of all Safety Letters / Safety Updates from other studies with MEDI4736 reported to regulatory authorities.

11.8 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.31 web-based safety monitoring utility.

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. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial BR.31 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 other sites:
Investigators/Sponsors must notify their Research Ethics Boards (REBs) of events according to local policies and ensure that a record of submission and acknowledgement be retained in the Site Files.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0.
- Disease relapse or new primary invasive malignancy as defined in Section 10.0.
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. 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.

12.2 Duration of Protocol Treatment

Treatment will continue for one calendar year (12 months) from the date of the first infusion. Patients who have relapsed disease or new invasive primary malignancy will discontinue study treatment at the time relapse/new invasive primary malignancy is documented clinically, radiographically and/or pathologically (see Section 10).

12.3 Therapy After Protocol Treatment is Stopped

Anti-cancer therapy after protocol treatment is stopped in the event of relapse/new invasive primary malignancy is at the discretion of the investigator. Subsequent anti-cancer therapy will be collected on the CRFs.

12.4 Follow-up Off Protocol Treatment

All patients will be seen at 4 and 12 weeks from the date of the last omitted or administered infusion, even if the decision to permanently discontinue therapy is made part-way through the cycle. Thereafter, patients without evidence of disease relapse or new primary malignancy will be followed as per schedule outlined in Section 9.2. Patients that have relapsed disease or new primary malignancy as per definitions in Section 10 will continue to be followed until death as outlined in Section 9.3.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 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 de-identified 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 IV (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 centre's 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.

13.2 Central Radiology Review

Central radiology review of equivocal cases by a review committee may be conducted in a blinded manner. A retrospective radiology review of all cases may also be undertaken if required by a regulatory authority.

13.3 Central Pathology Review

There is no prospective central pathology review planned for this study. A retrospective review may be undertaken.

13.4 Tissue Collection

A detailed Correlative Studies Manual will be provided at centre activation, which will include details regarding sample preparation, handling and shipping. (Tissue sample collection for correlative studies other than PD-L1 estimation will *not* be conducted in China sites.)

13.4.1 *Evaluation Of PD-L1 Expression Must Be Undertaken Prior to Randomization But After Registration*

Determination of PD-L1 expression by immunohistochemistry (IHC) requires that tissue blocks (tumour and normal tissue, formalin fixed, paraffin embedded) from existing tumour specimens be submitted to a central reference laboratory for analysis.

This representative block of the tumour tissue and adjacent normal tissue (for reference purposes for the planned sequencing of tumour samples), each measuring at least or greater than 1 x 1 x 0.4 cm or representative archival surgical pathology blocks is a mandatory part of this trial and must be submitted after registration. Submission of slides only will NOT be acceptable for PD-L1 expression assessment. Results of the PD-L1 testing are required prior to randomization.

Further details of the processing, preparation and shipment of tissue blocks are provided in the Correlative Studies Manual. Note: As the study starts, PD-L1 expression testing may be centralized in one laboratory in the USA, until laboratories in Europe and Australasia are set up.

Tumour tissue will be evaluated for PD-L1 expression (proportion of expressing cells and intensity and type of cells expressing PD-L1). Exploratory studies of PD-L1 expression including evaluation of cut points in relation to study outcome data will also be undertaken.

Only blocks will be accepted; slides are NOT acceptable. Participating sites and pathologists must commit to submitting tissue blocks for this study, and to inform CCTG immediately if changes in local policies preclude this. 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 after preparation. This will optimize the amount of tissue available to investigators and permit the preservation of the block submitted. As this study enrols only patients who have had curative resections, it is anticipated that sufficient tumour samples would be retained at the participating site. Centres who need to deposit samples at the time of surgery in a research tissue repository in order to release blocks for this study need to ensure that this is done for any patient who may be enrolled in this study. 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.

Following successful randomization of the participant, the tissue blocks will be forwarded to the appropriate tissue repository for the study. For patients that are not randomized to the study, the tissue blocks will be returned to the site.

13.4.2 *EGFR and ALK Tumor Mutation Assessment*

EGFR and ALK status will be determined retrospectively by central testing in advance of the interim analysis data cut-off. Tumor biopsy at diagnosis or resected tumor tissue sample will be used for assessing EGFR mutation and ALK translocation status where possible.

EGFR testing will be performed by a well-validated test such as Cobas® EGFR Mutation Test v2 real-time PCR that identifies 42 mutations in exons 18, 19, 20 and 21 of the EGFR gene. ALK testing will be performed using immunohistochemistry (IHC) with reflex to fluorescence in situ hybridization (FISH) testing of ALK gene rearrangements in an event of IHC indeterminate result. In an event where central testing for EGFR or ALK is unknown including reflex ALK FISH test, local test results may be used if available to determine EGFR and or ALK status. If the local laboratory will perform the test, a well-validated, local regulatory-approved kit must be used.

The definitions of the key analysis sub-populations are based on excluding patients confirmed as having an EGFR exon 21 L858R mutation and/or an EGFR exon 19 deletion (denoted as "EGFR+"), or ALK gene rearrangements (denoted as "ALK+").

13.4.3 *Exploratory Tumor Biomarker Assessments*

The tissue may be used by researchers now or in the future to better understand the nature of non-small cell lung cancer and how patients respond to treatments. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. 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. This process is applicable to all tissues collected as part of this study, irrespective of the location of the Tissue/Tumour Bank (see Section 13.4.6).

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

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

Planned priority assays may include but are not limited to:

- Evaluation of lymphocyte infiltration including subtypes by immunohistochemistry
- Next generation sequencing to correlate mutations with PD-L1 status and outcome
- Validation of previously reported prognostic gene signatures
- Discovery of immune related gene signatures

Immunohistochemical techniques will be used to evaluate Tumour Infiltrating Lymphocytes (TILs) which are known to be prognostic, and provide a unique opportunity to evaluate their role as a predictive factor for immune-based therapies.

We plan to study the prognostic role of the 1000 most frequently mutated genes from The Cancer Genome Atlas (TCGA) set using custom capture probes (Illumina) and targeted parallel sequencing technique. Whole exome sequencing using the Next Generation Sequencing (NGS) technologies may be performed if feasible. These approaches will fast-track the identification of novel prognostic/predictive markers in patients with completely resected NSCLC.

A number of prognostic gene expression signatures have been published including from JBR10, but have not yet been shown to be predictive and allow for selection of patients most likely to benefit from adjuvant chemotherapy. There are no predictive signatures proposed for immunotherapies in this setting *[Zhu 2010]*. Using RNA extracted from FFPE tissue from submitted blocks, we will use methods such as Nano String and other assays optimized to measure RNA isolated from FFPE samples to test the prognostic and predictive (for ACT) ability of published gene signatures. In addition to the validation of existing signatures, we will also train and validate new signatures from FFPE tissue using these methods. The models selected in the training phase will be applied to an independent validation set of patients by the statistical center. A sensitivity analysis will also be performed in studying the distribution of the prognostic value of the different signatures with resampling techniques.

For China sites, patients will be registered prior to submission of 10-15 (minimum 10) tumour slides each of 4 microns (4 μm) thickness for PD-L1 estimation. The tumor slides will not be used by researchers now or in the future for any correlative studies other than PD-L1 estimation and EGFR/ALK assessment. For patients that are not randomized, slides will not be returned to the site, but will be destroyed.

13.4.4 *Blood, Serum and Plasma*

Blood, serum and plasma will be collected pre-randomization, at the time discontinuation of MEDI4736/placebo and at the time of relapse/new primary malignancy at participating sites. Blood and fluid samples collection (correlatives) will *not* be conducted in China sites.

Anti-tumour immune responses are key contributors to the anti-tumour effects of anti-PD-L1 therapies. Serological responses (cytokines, antibodies and metabolites) provide rich sources of correlative data that can be used to understand the biological consequences of this novel therapy and may provide important biomarkers that will facilitate future patient management.

Assays may include but are not limited to:

- IFN-γ, tumour necrosis factor-α, IL-2, IL-6, IL-10, IL-8, and IL-12
- Circulating ligand soluble PD-L1
- Circulating DNA
- Micro-RNA
- Metabolic changes associated with treatment
- Anti-tumour antibody development
- Polymorphisms
- Circulating PD-L1
- Anti-drug antibodies

IFN-γ, tumour necrosis factor-α, IL-2, IL-6, IL-10, IL-8, and IL-12 will be assayed from patient sera using commercially available specific ELISA tests (R&D Systems) or with the Luminex MAGPIX platform. These have been demonstrated to have a sensitivity for detection of the protein of interest in the pmol range, and have been shown to have no cross-reaction with closely related proteins. Levels will be quantitated in serum in duplicate for each sample by comparison to internally generated standard curves using recombinant proteins. The data generated will be analyzed to determine whether baseline levels are predictive of outcomes, and whether changes pre- and post- treatment and at relapse can be correlated with outcomes such as survival.

Circulating tumour DNA (ctDNA) is a promising tool that will aid the development of new drugs especially in the palliative setting or where access to tumour tissue is difficult. We will evaluate for common and relevant mutations, and compare the results to the tissue genomic profiling which will be available on all patients. In addition, preliminary data suggests that changes in ctDNA levels may correlate with relapse, or enable the detection of mutations that may contribute to treatment failure *[Bettegowda, 2014]*.

Several studies have identified circulating microRNAs (miRNA) as non-invasive markers of malignancy. miRNA are small RNA molecules of 21-23 nucleotides that bind with imperfect complementarity to sequences in specific mRNA targets and typically silence their expression and have been implicated in tumour progression by modulating oncogenic and tumour suppressor pathways. This study will explore known circulating oncogenic miRNA profiles by low-density PCR arrays and/or equivalent techniques and correlate with treatment outcomes.

Metabolic changes associated with treatment will be measured in sera using liquid chromatography-mass spectrometry. Anti-tumour antibodies will be characterized using a phage-display methodology with a phage expression library derived from a collection of human tumours.

Genetic polymorphisms may play a role in both lung cancer risk and outcomes. Polymorphisms may predict differences in behaviour of the cancer, immune mechanisms, or cancer drug metabolism. We will collect a baseline whole blood sample to enable exploratory testing of polymorphisms known or suspected to be associated with the outcomes of completely resected NSCLC , platinum based ACT as well as immune pathways and response to immunotherapies *[Broderick 2009; Horgan 2011; Danesi. 2009]*.

Other studies that may be considered include, but are not limited to: serum EGFR extracellular domain (ECD), serum HER2 ECD, E-cadherin ELISAs, TGF-α and HGF, as well as antidrug antibodies, s-PD-L1, and or MEDI4736 levels.

13.4.5 *Pharmacokinetics*

Pharmacokinetic studies are planned to enable pharmacokinetic/pharmacodynamics correlations.

The following samples should be collected ONLY for those countries participating in this portion of the study.

Blood Collection Type	Timing*			
	Week 0 (pre-dose)	Week 4 (pre-dose)	Week 24 (pre-dose)	90 days post last received dose
PK Serum		X	X	X
ADA Serum	X	X	X	X

* For pre-dose, collection should be ≤ 1 hour before start of infusion.
** At 90 days post last received dose, the blood collection can be +/- 7 days from the date they are required to accommodate visit schedule.

Please refer to the BR.31 Pharmacokinetic and Anti-Drug Antibodies Sampling Manual.

13.4.6 *Tumour and Tissue Banks*

Blocks and all other samples will be carefully banked in one of two banks. Samples from France will be banked at the IFCT Repository. No tissue samples/slides will be banked from China sites.

All other samples will be banked at the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario, or at applicable regional banks as detailed in the separate Correlative Studies Manual. Diagnostic pathology reports are received as part of the supporting documentation required for this trial.

There will be one laboratory manual for the study with consistent procedures irrespective of the Repository.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This is an international multicenter, double blinded, placebo controlled, prospective, adjuvant phase III randomized trial of MEDI4736 or placebo in patients with completely resected stage IB (≥ 4cm), II or IIIA NSCLC. Patients will be randomized to receive either MEDI4736 or placebo in a 2:1 ratio using the dynamic minimization method stratified by:

- stage (IB (≥ 4cm) vs II vs IIIA)
- pre-treatment PD-L1 expression (A [≥ 50%] vs. B [25-49%] vs. C[1-24%] vs. D [< 1%])
- adjuvant platinum based chemotherapy (≥ 300 mg/m^2 cisplatin/equivalent vs. < 300 mg/m^2 vs. no chemotherapy)
- accruing centre
- nodal sampling/dissection conducted in accordance with the European Society of Thoracic Surgeon (ESTS) guidelines (yes vs. no)

For analysis of study objectives described below, six patient sub-populations are defined according to the PD-L1 expression stratum as determined at randomization, and EGFR/ALK mutation status determined retrospectively. The "EGFR-/ALK-" sub-population excludes only those with common activating EGFR mutations (defined as exon 21 L858R mutation or exon 19 deletions) or with ALK gene rearrangements (ALK+). The six study sub-populations are as follows:

- PD-L1 TC ≥ 25% and EGFR-/ALK-
- PD-L1 TC ≥ 1% and EGFR-/ALK-
- All EGFR-/ALK-
- All PD-L1 TC ≥ 25%
- All PD-L1 TC ≥ 1%
- All randomized patients

Exclusion from the "EGFR-/ALK-" sub-populations will be on the basis of confirmed mutation status only, i.e. unknown mutation status is treated as not having the mutation for the purpose of defining analysis sub-populations.

The primary objective is to assess the effect of MEDI4736 by comparing disease-free survival (DFS) between the two treatment arms in patients with NSCLC that is PD-L1 expression TC ≥ 25% and EGFR-/ALK-.

Secondary objectives will evaluate study treatment effect:

- To compare the DFS in the MEDI4736 arm to the placebo arm in the remaining 5 patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To compare the overall survival (OS) in the MEDI4736 arm to the placebo arm in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To compare lung cancer specific survival in the MEDI4736 arm to the placebo arm in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To evaluate the nature, severity, and frequency of toxicities, between the two treatment arms.

- To evaluate the quality of life between the two treatment arms in the six patient sub-populations defined by PD-L1 expression levels and EGFR/ALK status.
- To determine the survival benefits participant's judge necessary to make adjuvant immunotherapy worthwhile, and the factors influencing their preferences
- To determine the incremental cost effectiveness and cost utility ratios for MEDI4736.
- To evaluate the prognostic and predictive significance of PD-L1 expression.
- To evaluate changes in plasma/serum cytokines and other blood and tissue based biomarkers after treatment with MEDI4736 or placebo and at time of disease relapse/new invasive primary malignancy.
- To explore polymorphisms that may be associated with outcomes.

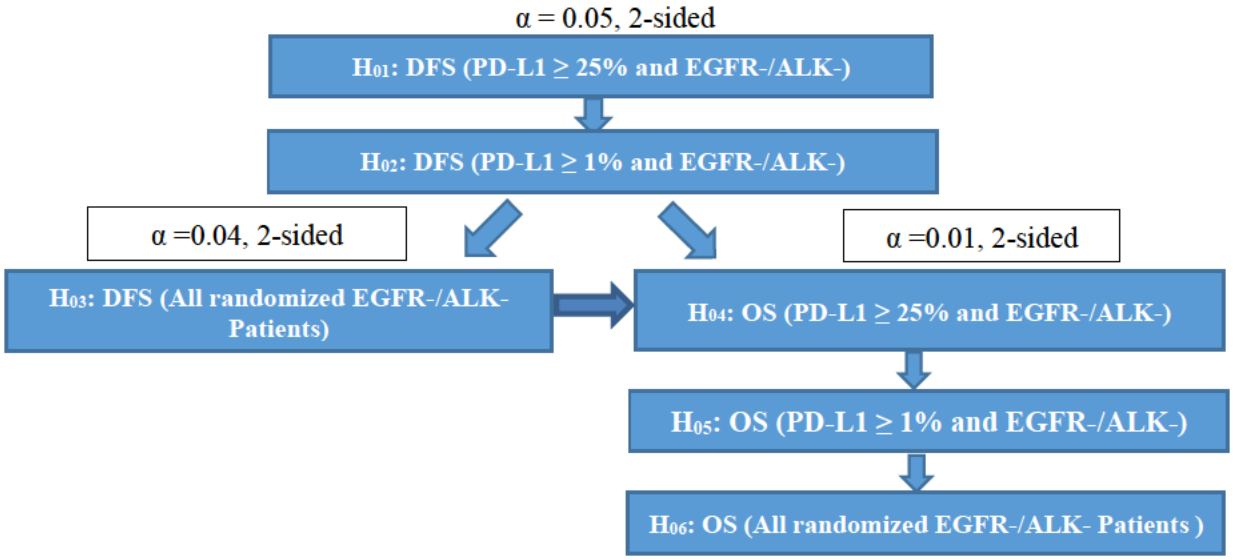
14.2 Sample Size, Power and Duration of Study

The sample size for this study is determined to compare DFS in the sub-population of NSCLC EGFR-/ALK- patients with PD-L1 expression ≥ 25%. The expected 5-year DFS rate of patients on the placebo arm was estimated to be 51%, and 5-year expected OS rate of placebo patients was estimated as 58%.

In order to have 85% power to detect a 35.5% reduction in the risk of disease relapse/new primary malignancy with MEDI4376 (i.e. a hazard ratio (HR) for DFS of 0.645) in the PD-L1 ≥ 25% and EGFR-/ALK- patients using a 2-sided 5% significance level test, the required sample size for this study is estimated as 1360 patients (expected to include approximately 450 PD-L1 ≥ 25% and EGFR-/ALK- patients). Assuming a 5-year patient accrual period, the required number of DFS events for the primary DFS analysis (212 relapses/new primary malignancies or deaths in PD-L1 ≥ 25% and EGFR-/ALK- patients) is estimated to be observed with another 4 years of follow up. At the time of this analysis, it is anticipated there will be approximately 320 DFS events in PD-L1 ≥ 1% EGFR-/ALK- patients, which can provide 85% power to detect a HR of 0.7. The sample size was calculated with a planned interim analysis testing for superiority of the study treatment.

Testing treatment effect on DFS in the PD-L1 ≥ 1% and EGFR-/ALK- sub-population, in the all EGFR-/ALK- sub-population; and on OS in the three sub-populations of EGFR-/ALK- patients are key secondary objectives. To control the trial-wise type I error at 5%, a hierarchical testing strategy will be used. The order of the tests is depicted in the figure below. The tests for DFS will be performed using the Lan-DeMets error spending function with O'Brien-Fleming type boundaries with 2 analyses planned at information fractions of around 0.75 and 1 for DFS. The Type I error will be recycled according to the method of *"Multiple testing in group sequential trials using graphical approaches"* as proposed by Willi Maurer and Frank Bretz *[Maurer 2013]*. For the hierarchical test of the PD-L1 ≥ 25% EGFR-/ALK- and PD-L1 ≥ 1% EGFR-/ALK- sub-populations, the tests will be performed at the same significance level for each test at the time in the pre-specified order and further testing is stopped at the time of the first non-significant result. The formal test of DFS in the all EGFR-/ALK- sub-population and OS in the PD-L1 ≥ 25% EGFR-/ALK- will only be performed when the tests on DFS are positive in both PD-L1 ≥ 25% and EGFR-/ALK-, and PD-L1 ≥ 1% and EGFR-/ALK- sub-populations, the overall hierarchical test strategy for group sequential tests will be conducted according to the method of *"Hierarchical testing of multiple endpoints in group-sequential trials"* as proposed by Glimm, Maurer and Bretz *[Glimm 2010]* with a separate Haybittle-Peto type spending function for OS. The alpha splitting and recycling strategy are given in Figure A below.

Figure A: Hierarchical Testing and Type I Error Recycling Plan



It has been observed that there were around 38%, and 58% of all randomized patients with PD-L1 ≥ 25% and PD-L1 ≥ 1% expression, respectively.

14.3 Study Endpoints and Analysis

The primary endpoint is DFS, which is defined as the time from the date of randomization to the date of first documented disease relapse or the occurrence of a new invasive primary malignancy or death from any cause. Patients who are alive and disease/new invasive primary malignancy-free at the time of each analysis will be censored at their last disease assessment date.

All randomized patients in the pre-specified PD-L1 expression and EGFR/ALK status sub-populations will be included in the analysis of DFS. The patterns of the relapses and new primary malignancies will be summarized by treatment arms. Kaplan-Meier curves for proportions of event-free patients in each treatment arm will be displayed. The 95% confidence intervals for the median of time to event endpoints will be computed using the method of Brookmeyer and Crowley. In the primary analysis of DFS within different PD-L1 expression and EGFR/ALK status defined sub-populations, DFS between the two treatment arms will be compared using the log-rank test stratified by selected stratification factors at randomization. Treatment effect and its confidence interval at the specified significance level of the test at the time of the analysis will be estimated from Cox regression model stratified by the selected stratification factors at randomization. For comparison within the PD-L1 ≥ 25% and EGFR-/ALK- sub-population, the selected stratification factors are disease stage (IB/ II vs. IIIA) and adjuvant platinum-based chemotherapy (≥ 300 mg/m^2 cisplatin/equivalent vs. < 300 mg/m^2 vs. no chemotherapy); while for the PD-L1 ≥ 1% and EGFR-/ALK- sub-population and the all EGFR-/ALK- sub-population, the selected stratification factors are: disease stage (IB/ II vs. IIIA), pre-treatment PD-L1 expression (≥ 25% vs. 1-24% vs. < 1% as appropriate) and adjuvant platinum-based chemotherapy (≥ 300 mg/m^2 cisplatin/equivalent vs. < 300 mg/m^2 vs. no chemotherapy). In addition, the effect of study center and other potential prognostic factors, such as age and gender, on DFS and OS will be assessed using Cox regression. The test based on cumulative sums of martingale residuals *[Lin 1993]* will be used to check the Cox regression model assumption.

The tests at interim analysis and final analysis and the corresponding stopping guidelines for DFS are determined by the Lan-DeMets error spending function with O'Brien-Fleming type boundaries. In addition, at the final analysis, the stratified Cox regression model with study treatment and PD-L1 expression defined sub-group and their interaction term included will be undertaken to test if PD-L1 expression levels predicts study treatment effect in the patients' population. A similar analysis on EGFR and ALK status will also be explored. We will provide the estimate of treatment effect and its 95% C.I. in the PD-L1 expression (≥ 25%, 1 to 24% and < 1%) by EGFR/ALK status (EGFR-/ALK- and EGFRm/ALK+) subgroups as well.

OS is a key secondary endpoint, defined as the time from the randomization to the date of death of any cause, or censored at their last known alive date. Overall survival will be hierarchically tested in each of the pre-specified PD-L1 expression TC score and EGFR-/ALK- sub-population as in the previously specified figure. If the tests of DFS are significant at interim analysis or final analysis, OS will be analyzed according to the Haybittle-Peto type test, and the final analysis on OS will be performed at a pre-defined analysis time point, i.e. around five years after the last patient was randomized to the trial. All analyses performed for DFS will be performed for OS.

Lung cancer specific survival (CSS) is another secondary endpoint of the trial, defined as the time from the date of randomization to the date of patients died of lung cancer, or censored at the last contact date. A competing risk analysis will be used to test for difference in CSS between the two treatment arms.

Although PD-L1 expression as measured by immunohistochemistry is hypothesized to be a potential predictive marker, this is as yet not validated in either the adjuvant or palliative settings. Further, the cut-off defining PD-L1 positivity has not been validated. This trial will also explore the utility of PD-L1 as a predictive biomarker as well as the optimal cut-off for positivity.

Per CCTG standard procedures, a detailed Statistical Analysis Plan (SAP) will be prepared and finalized before performing any statistical analysis by treatment group.

14.3.1 *Interim and Final Analysis of DFS in PD-L1 Expression Sub-populations in EGFR-/ALK- patients*

We will perform an interim analysis on DFS in the different PD-L1 expression and EGFR/ALK sub-populations when approximately 159 DFS events have been observed in the PD-L1 ≥ 25% and EGFR-/ALK- sub-populations, estimated to occur approximately 6.9 years after the time of the first patient accrued to this trial. Based on the Lan-DeMets error spending function with O'Brien-Fleming type of boundaries, with an information fraction of 0.75 for illustration (the actual information fraction will use the observed number of events at the interim), we would claim significant treatment effect if a p-value of 0.0193 or less is observed. Otherwise, all patients would continue to be followed until the final analysis, when a significance level of 0.044 would be used for the final test. The same stopping rules would apply for the PD-L1 ≥ 1% and EGFR-/ALK- sub-population. For the DFS test in the all EGFR-/ALK- sub-population, it will be tested if the tests in both PD-L1 ≥ 25%, EGFR-/ALK- and the PD-L1 ≥ 1%, EGFR-/ALK- are positive. The adjusted significance levels would be based on the same information fraction as for the previous tests, but applied to an overall alpha level of 4% two-sided, e.g. 0.0144 and 0.0357 would be used at IA and final analysis for an information fraction of 0.75.

14.3.2 *Interim and Final OS Analysis*

Interim and final OS analysis in PD-L1 expression sub-populations in EGFR-/ALK- patients:

The analysis on OS will performed using the Haybittle-Peto type of boundaries with three potential analysis time points. Tests for different PD-L1 expression level sub-populations and EGFR/ALK status will be hierarchically tested in the pre-specified order. After each prior sub-population test is rejected, the test for OS in the next population will be performed with the stopping boundary significance level of 0.001 at the time point of interim analysis. The final analysis on OS will be performed after the last patient has been followed up for 5 years.

The first potential time point for OS analysis will be at the time of the DFS interim analysis. If DFS tests are significant for both PD-L1 ≥ 25% EGFR-/ALK-, and PD-L1 ≥ 1% EGFR-/ALK- sub-populations at this analysis, an interim analysis on OS will also be performed. The significance level of 0.001 will be used.

If DFS is not significant at the time of the interim analysis but is significant at the final DFS analysis for both the PD-L1 ≥ 25% EGFR-/ALK-, and PD-L1 ≥ 1% EGFR-/ALK- sub-populations, the test for significance on OS will also be evaluated with significance level of 0.001.

If the test on DFS is negative for either of the PD-L1 ≥ 25% EGFR-/ALK-, and PD-L1 ≥ 1% EGFR-/ALK- sub-populations, then the analysis on OS for any positive subgroup will be supportive/descriptive with no interpretation of statistical significance, potentially, at the time of the final analysis of DFS and/or after 5 years of the last patients accrued to the trial. If tests for DFS are positive for both PD-L1 ≥ 25% EGFR-/ALK-, and PD-L1 ≥ 1% EGFR-/ALK- populations, the final test for OS will be performed at around 5 years after the last patient has been randomized to the trial. The adjusted significance level will be determined according to whether the test on DFS in the all EGFR-/ALK- sub-population is positive allowing the 4% type I error to be recycled (0.0498 for 5% overall alpha) or not (0.0096 for 1% overall alpha).

Subgroup analyses

Subgroup analyses will be conducted in the following subgroups (but not limited to):

- Sex (male vs. female)
- Age at randomization (< 65 vs. ≥ 65 years of age)
- Race (Caucasian vs. Hispanic vs. Black vs. Asian vs. others)
- Disease Stage (IB (≥ 4cm) vs. II vs. IIIA)
- Pre-treatment PD-L1 expression level (PD-L1 ≥ 25% vs. PD-L1 1-24% vs. PD-L1 < 1%)
- Adjuvant platinum-based chemotherapy (≥ 300 mg/m^2 cisplatin/equivalent vs. < 300 mg/m^2 vs. no chemotherapy)
- Nodal sampling/dissection conducted in accordance with the European Society of Thoracic Surgeons (ESTS) guidelines (yes vs. no)
- EGFR mutation status (EGFR mutations with exon 21 L858R or exon 19 deletions vs other EGFR mutations vs no EGFR mutations)
- ALK mutation status (ALK+ vs. ALK-)

Patients with missing data for a subgroup variable (e.g. unknown EGFR or ALK mutation status) will be excluded from the subgroup analysis for that variable only.

Other baseline variables may also be assessed if there is clinical justification. The purpose of the subgroup analyses is to assess the consistency of treatment effect across important disease and patient demographic factors. If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 10 events in a subgroup), it will not be performed for the subgroup.

Sensitivity analysis on OS: Due to the potential issue of the delayed treatment effect, i.e., the non-constant treatment effect, a sensitivity analysis on comparison of the restricted mean overall survival time (RMST) within 5 years of study will be conducted between the 2 study treatment arms. Estimate of the difference of RMSTs between the 2 treatment arms and its 95% C.I. will be given.

14.3.3 *Quality of Life Analyses*

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

Changes of the quality of life scores while on treatment versus baseline will be examined using analysis and descriptive statistics. Specific time points will be checked to explore treatment side effect on patients QoL, and the longtime benefit of the study treatment. In addition, baseline scores will be compared using a Wilcoxon rank sum test, and a pattern mixture model *[Little 1995]* identifying drop-out patients as a special category, will be performed to evaluate the effect of missing data. Additional analyses will be conducted using CCTG standard analysis programs.

14.3.4 *Economic Analyses*

The purpose of the CCTG economic evaluation is to determine the incremental cost-effectiveness and cost-utility of MEDI4376 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) determine an incremental cost effectiveness ratio reported as a cost per life-year (LY) gained of MEDI4376 vs. Placebo. 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) determine an incremental cost utility ratio in cost per quality-adjusted life-year (QALY) gained of MEDI4376 vs. Placebo. 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 *[Shaw 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). A cost-effectiveness acceptability curve will be generated through bootstrapping samples.

The economic data analysis will only include data from groups/regions that participate in the economic study.

14.3.5 *Patient Preference Sub-study*

The specific objectives of this sub-study are to determine the:

- benefits judged necessary to make MEDI4736 treatment worthwhile
- factors influencing the preferences of patients
- differences in preferences before and after patients have experienced treatment with MEDI4736
- differences in preferences between patients who do and do not have MEDI4736
- differences in preferences according to country, gender, previous adjuvant chemotherapy, and other characteristics.

Based on median benefits judged sufficient to make adjuvant chemotherapy worthwhile in a recent study of 122 patients referred for consideration of adjuvant chemotherapy after resection of stage 1-3 NSCLC, we hypothesize that the median benefit judged sufficient will be < 3% absolute improvement in survival rates and < a 9 month improvement in median survival times at either 3 years or 5 years.

Participating patients from Australia, New Zealand and Canada (as well as any other countries identified) will complete a preferences questionnaire before randomization, and at their four week follow up visit after discontinuing protocol therapy. The questionnaire will determine the smallest improvements in survival rates and survival times that participants judge necessary and sufficient to make the inconvenience and adverse effects of adjuvant immunotherapy worthwhile.

A sample size of 400 participants in total will provide 95% CI of ± 5% or less for the estimated proportion of participants judging a given survival benefit sufficient to make adjuvant immunotherapy worthwhile. A sample size of 200 participants per country will provide over 80% power to detect a true absolute difference of 14% between 2 countries in the proportions of participants judging a given survival benefit sufficient. A multivariable model including 400 participants is sufficient to include 20 candidate correlates of preferences. Our previous multivariable models assessing correlates of preferences have included 5 or fewer significant variables.

14.4 Safety Monitoring

All patients who receive at least one dose of MEDI4376/placebo will be included in the safety analysis. Descriptive summary tables will be presented on safety parameters by treatment arm. Toxicity rates will be compared between treatment arms using the Fisher's Exact Test or Chi-square test, as needed. There will be safety monitoring by the CCTG Data Safety Monitoring Committee (DSMC) every 6 months.

Immune adverse events of special interest will be analysed with p-values including: pneumonitis, endocrinopathies, dermatologic (rash/pruritus) and hepatic (elevation of transaminases/bilirubin).

14.5 Patient Cohort

The trial will enroll all eligible patients in the whole population irrespective of PD-L1 expression status. With an observed prevalence of 0.38 of PD-L1 $\geq$ 25% (strata A plus B) in the population, we will have around 530 PD-L1 $\geq$ 25% (approximately 450 of which will be EGFR-/ALK- patients). Meanwhile, it was observed that 58% of patients exhibited a PD-L1 expression level of $\geq$ 1%. The $\geq$ 25% cut-point has been analytically validated for analyses. The precise incidence of PD-L1 expression and EGFR/ALK status in the planned population is unknown. Enrollment to each PD-L1 expression cohort (positive, negative) will be evaluated by the Trial Statistician every 6 months, and any adjustment to sample size or subgroup size will be approved by DSMC and detailed in a protocol amendment.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

15.1.1 The results of this study will be published. This trial will be published under a group title (LINC) but with naming of a limited number of individual authors. The following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the Trial Committee members may be credited as authors depending upon their level of involvement in the study.
- Additional authors 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 discussed and agreed with Participating Groups.

In the event of a separate paper dealing with the quality of life outcomes, correlative studies or health economics outcomes, the first author will generally be the Chair of the relevant Working Group.

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

> "A study developed and coordinated by the Canadian Cancer Trials Group in conjunction with Intergroupe Francophone de Cancerologie Thoracique (IFCT), the Central and East European Oncology Group, the National Cancer Institute, Naples, the Dutch Society for Pulmonology and Tuberculosis (NVALT) the Korean Cancer Study Group, the Fundación GECP, the West Japan Oncology Group (WJOG), Chinese Thoracic Oncology Group (CTONG) and the Australasian Lung cancer Trials Group & NHMRC Clinical Trials Centre. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

Other supporting groups and agencies will be acknowledged.

15.2 Responsibility for Publication

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

Dissemination of Trial Results

CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted in Canada 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).

This trial is being conducted under an IND or related arrangement in other countries and all applicable Laws, Regulations and Policies must be followed.

16.2 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 must 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.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an 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. It is recommended that centres 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.

16.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the pregnant female is not a participant in the main trial, consent should be obtained via use of the exposure/pregnancy follow-up consent form.

In the case of information collected about a newborn, consent should be provided by the legal guardian. In cases where the legal guardian is the participant in the main trial, consent is obtained via the main consent. If the legal guardian is not the trial participant, consent should be obtained via the exposure/pregnancy follow-up consent.

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

16.4 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.

16.5 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.

16.6 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.

16.7 On-Site Monitoring/Auditing

In addition to the routine review of case report forms and supporting documents sent to the central office, site monitoring will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors will require access to patient medical records to verify the data, as well as pharmacy, essential document binders, standard operating procedures (including electronic information) and ethics documentation.

Your site may be subject to an inspection by regulatory authorities and audits by CCTG, Astra Zeneca, CCTG designated organizations, or by the Group responsible for oversight of your site.

16.8 Case Report Forms

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

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the BR.31 area of the CCTG web-site: www.ctg.queensu.ca.

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study	On treatment Prior to each infusion	On treatment – every 12 weeks	End of Treatment visit (4 weeks after last omitted or administered infusion)	Follow Up - 12 week visit (12 weeks after last omitted or administered infusion)	Follow-up prior to disease event – Every 12 weeks until 2 years from randomization, then every 6 months until 3 years from randomization then annually	Follow up after disease event – Every 6 months until 3 years from rand. then annually
Physical[32]							
History	X	X		X	X	X	X
Physical exam (height, weight, BP, pulse)	X	X		X	X	X[34]	X[34]
Smoking history	X	X			X	X	X
ECOG	X	X		X	X	X	X
Concomitant medications	X	X		X	X		
Hematology[1]							
CBC, differential	X	X		X	Only as clinically indicated or to follow related AE until resolution to grade 0-1		
Biochemistry[1]							
AST[33], ALT[33], Alk Phos, Bili, Albumin, Serum Cr[2], Random glucose or fasting glucose, Amylase[29], Lipase[29]	X	X		X	Only as clinically indicated or to follow related AE until resolution to grade 0-1		
Creatinine clearance	X						
TSH[3]	X	X[4]		X[5]	X[5]	As clinically indicated or to follow related AE until resolution to grade 0-1	
CRP	X						
INR/APTT	X	As clinically indicated					
Radiology							
CT chest and upper abdomen (must include adrenal glands)	X		X	X[6]	X[7]		X[8]
CT or MRI brain[9] PET scan thorax[9]	X	As clinically indicated					
Other imaging	X[10]	As clinically indicated[11]					
Other Investigations							
ECG	As clinically indicated						
Pregnancy test (if applicable)	X[12]	X[12]		X[12]	X[12]	X[12]	X[12]
Lung function tests (FEV1, FVC, TLCO[13] and SaO2 or SpO2 on room air)	X[14]	X[15]		X[15]	X[15]	X[15]	X[15]
Urinalysis	X	As clinically indicated			As clinically indicated		
LVEF [16]	X						
Adverse Events							
Continuously graded and recorded according to CTCAE v4.0	X	X		X	X[17]	X[17]	X[17]
Quality of Life							
EORTC QLQ-C30 + QLQ-LC13 + trial specific checklist	X	X[18]			X[19]	X[19]	
Preferences for Adjuvant Immunotherapy[20]	X				X[21]		

table continues on next page ...

Required Investigations	Pre-study	On treatment Prior to each infusion	On treatment – every 12 weeks	End of Treatment visit (4 weeks after last omitted or administered infusion)	Follow Up - 12 week visit (12 weeks after last omitted or administered infusion)	Follow-up prior to disease event – Every 12 weeks until 2 years from randomization, then every 6 months until 3 years from randomization then annually	Follow up after disease event – Every 6 months until 3 years from rand. then annually
Economics[22]							
EQ-5D	X	X[18]		X[23]	X[24]	X[24]	
Resource Utilization Assessment		X			X[30]	X[30]	
Correlatives							
Archival tissue blocks[31]	X						
Whole blood, serum, plasma[26]	X			X			X[25]
Serum for PK and ADA sampling[27]		X[28]			X		

1 Bloodwork Timing: Bloodwork done prior to randomization does not need to be repeated prior to first treatment. After the first treatment, 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 XIII 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.

2 Serum Creatinine is not required pre-study

3 If TSH is abnormal, both T3 and T4 should be measured (both are recommended but at least one of T3 or T4 is mandatory if TSH is abnormal).

4 Prior to infusions at week 4, 12, 24, 36 and 48. May be done up to 7 days prior to scheduled infusion.

5 May be done within 7 days prior to visit.

6 Only required if scheduled q12 weekly scan corresponds to End of Treatment visit timing.

7 Every 12 weeks for a total of 2 years from randomization, then at months 30 and 36 from randomization, and then annually until final DFS analyses performed. Thereafter according to local policy.

8 Only as clinically indicated to follow toxicity to resolution (e.g. pneumonitis)

9 Only if not done prior to surgery.

10 Required only if suspicious signs/symptoms are present.

11 When relapse is first documented at any site, complete restaging is required to identify all sites of relapse.

12 Pregnancy test only required for WOCBP and should be repeated at investigator's discretion. Romania only: Pregnancy test only required for WOCBP and should be repeated on a monthly basis during treatment and then as per follow up visits.

13 TLCO (transfer factor of the lung for carbon monoxide) is the same as DLCO (total diffusing capacity for the lung) but should NOT be confused with the abbreviation "TLC" (Total Lung Capacity).

14 Strongly recommended. Sites may opt out after discussion with CCTG but is mandatory for sites who have not opted out.

15 Only if pulmonary symptoms or suspicious for pneumonitis.

16 MUGA or ECHO, only for patients with significant cardiac history.

17 Record on CRF only if related to MEDI4736/placebo.

18 Week 4, 12, 24, 36 and 48. Administer on day of planned infusion (up to 3 days prior to treatment is acceptable without prior approval) even if infusion is omitted.

19 At follow-up visit conducted 12 weeks after date of last infusion, then every 12 weekly visit until 2 years from randomization. See Appendix XII.

20 Australia/New Zealand and Canada only. Other countries as identified.

21 Preferences for adjuvant immunotherapy questionnaire should be completed at the 12 week post treatment visit. However, if missed, complete as soon as possible thereafter and enter in the next case report form.

22 Canada, Australia/New Zealand, Netherlands, France, Japan, Italy, Bulgaria, Romania and China only. Other countries as identified.

23 Only required if the End of Treatment visit is nearest visit following definitive relapse/new primary malignancy.

24 EQ-5D to be completed at follow-up visit conducted 12 weeks after the date of last infusion, then every 12 weekly visit until 2 years from randomization and at nearest visit following definitive relapse/new primary malignancy. See Appendix XII.

25 At time of disease relapse/new primary malignancy or within 4 weeks of disease relapse/new primary malignancy.

26 Blood and fluid samples collection (correlatives) will *not* be conducted in China sites.

27 Only for countries participating in pharmacokinetic and anti-drug antibodies sampling.

28 Prior to infusions at week 0, 4 and 24.

29 Amylase not required if local standard of care is to omit amylase if lipase is normal. Lipase not required if local standard of care is to omit lipase if amylase is normal.

30 RUA to be completed at each follow-up visit conducted 12 weeks after the date of last infusion, then every 12 weekly visit until 2 years from randomization, then every 6 months until 3 years from randomization then annually until definitive relapse/new primary malignancy and at nearest visit following definitive relapse/new primary malignancy. See Appendix XII.

31 Tumour tissue slides instead of tissue blocks will be submitted for sites in China.

32 History and Physical Exam Timing: History and Physical Exam done prior to randomization does not need to be repeated prior to first treatment. After the first treatment, pre-treatment history and physical exam 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).

33 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.

34 For patients who have not experienced a disease event, follow-up visits may be performed virtually after the final q12 weekly visit at 2-years post-randomization. For patients who experience a disease event while on treatment, follow-up visits after the 12-week post-treatment visit may be performed virtually. For patients who experience a disease event after the 4 and 12-week post-treatment visits have been performed, all subsequent 6-monthly and annual visits follow-up visits may be performed virtually. Physical exams are not required for virtual follow-up visits.

APPENDIX II - 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 III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

General and Drug Accountability

Investigational product (MEDI4736/placebo) should be stored in a secure area according to local regulations and under the storage conditions stipulated on the investigational product label. It is the responsibility of the Investigator to ensure that investigational product is dispensed only to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Drug accountability logs will be supplied on the BR31 website. Accountability will be maintained and each kit will be treated as a unit dose containers (i.e. vials will not be shared between patients).

The health care professional will determine the appropriate kit to dispense to the patient at the beginning of each cycle. This information will be recorded on the Drug Dispensing Log.

Destruction and Return of Investigational Product

- All unused or expired study medication, after accountability and reconciliation should be destroyed locally. Destruction of study medication must not take place without accountability and reconciliation by the monitor and the completion of a drug return/disposal form. A copy will be kept with the centre files.

- At the end of the study, it must be possible to reconcile delivery records with records of usage/returned stock by completion of the study drug accountability form. Any discrepancies must be accounted for. At the end of the study, after the monitor has completed drug accountability a copy will be kept with the centre files.

Distribution

Drug will be distributed by CCTG or designee to each participating centre. Start-up supplies will be dispatched following registration of the first patient. Full details regarding drug reordering will be supplied at study initiation and will involve the use of the CCTG website.

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. Quality of Life/Health Economics and Patient Preference Questionnaires will be completed on paper by the patient and the answers will be entered into EDC 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.31 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+	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission on Request To be uploaded immediately after request
Eligibility Checklist		Within 2 weeks of randomization	Signed consent form and tissue banking consent*, major surgical reports, diagnostic pathology reports and protocol mandated baseline radiology reports	Additional clinical, laboratory or imaging reports that may impact on decision regarding eligibility
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 off-treatment and relapse/new primary malignancy	Consent form*	
Treatment Report & Resource Utilization Assessment	Every 28 days*****	Within 2 weeks of end of cycle	Radiology reports for protocol mandated imaging and non-protocol mandated imaging done to assess disease status	Radiology reports for other non-protocol mandated imaging, additional clinical, laboratory or imaging reports that may inform evaluation of safety
End of Treatment Report	End of Treatment	Within 2 weeks of end of treatment		
12 Week Follow Up Report & Resource Utilization Assessment	12 weeks from the date of last omitted or administered infusion*****	Within 2 weeks of follow up visit	Radiology reports for protocol mandated imaging	Radiology reports for other non-protocol mandated imaging additional clinical, laboratory or imaging reports that may inform evaluation of safety
Follow-up Report & Resource Utilization Assessment	1) Every 12 weeks until 2 years from randomization, 30 and 36 months in year 3, then annually for patients that have not relapsed/had new primary. See Appendix XII. 2) Complete at time of first disease event (relapse or new primary malignancy) if after 12 Week Follow Up visit	Within 4 weeks of follow-up visit	Radiology reports for protocol mandated imaging	Radiology reports for other non-protocol mandated imaging, copies of additional clinical, laboratory or imaging reports that may inform evaluation of safety

table continues on next page ...

Electronic Folder	Required at	To be completed electronically	Supporting Documentation+	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission on Request To be uploaded immediately after request
Relapse/New Primary Malignancy Report	Upon disease relapse or new primary malignancy	Within 4 weeks of relapse/new primary malignancy	Disease event diagnosis imaging and pathology reports	Radiology reports for other non-protocol mandated imaging
Short Follow-up Report	Every 6 months after relapse/new primary until 3 years from randomization, then annually	Within 4 weeks of follow-up visit	Radiology reports for protocol-mandated imaging	Radiology reports for other non-protocol mandated imaging copies of additional clinical, laboratory or imaging reports that may inform evaluation of safety
Death Report	When patient dies***	Within 4 weeks of patient's death	Autopsy report, if performed	Additional clinical, laboratory or imaging reports that may inform evaluation of cause of death
Withdrawal of Consent	At time patient has withdrawn consent to participate in the clinical trial AND for further data submission	Within 2 weeks of withdrawal of consent	Signed and dated clinic note or letter to document patient's withdrawal of consent	
SAE Report**	At time of event and reported to CCTG	Within 1 working day		Additional clinical, laboratory or imaging reports that may inform evaluation of safety including, admission and discharge summaries/notes

\+ Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Please scan and upload all required source documentation into the Supporting Documents Upload tool (accessed through EDC) unless otherwise requested. Please refer to the slide set on the BR.31 website for guidance. 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.

* Canadian centres only: 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. All other centres: Submission of consent forms is not required, but they will be reviewed on site.

** See Section 11.0 Serious Adverse Event Reporting for details.

*** It is the investigator's responsibility to investigate and report the date and cause of death of any patient entered into this trial.

**** Blood and fluid samples collection (correlatives) will *not* be conducted in China sites. This folder is not required to be completed for sites in China.

***** Required even if relapse or new primary malignancy identified during reporting period.

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 web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

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

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

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

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

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

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

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

1. Preamble

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

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

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

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

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

2. Pretreatment Assessment

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

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

3. Assessments During Treatment

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (up to 3 days prior to treatment is acceptable without prior approval). 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 is not literate in 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.31**

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

On Treatment:

☐ Week 4 ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48

Off Treatment (from date of last infusion):

☐ 12 weeks ☐ 24 weeks ☐ 36 weeks ☐ 48 weeks ☐ 60 weeks ☐ 72 weeks

☐ 84 weeks ☐ 96 weeks

*Note: Questionnaire is not required to be completed at time of relapse/new primary malignancy or afterwards

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: __ __ - __ __ __ - __ __ __ __
dd mmm yyyy

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.31)

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 headaches?	1	2	3	4
47. Did you have swelling of your arms or legs?	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, eg: 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, as required by the schedule in the protocol (up to 3 days prior to treatment is acceptable without prior approval). 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.31**

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

On Treatment:

☐ Week 4 ☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48

Off Treatment (from date of last infusion):

☐ 12 weeks ☐ 24 weeks ☐ 36 weeks ☐ 48 weeks ☐ 60 weeks ☐ 72 weeks

☐ 84 weeks ☐ 96 weeks

☐ Following relapse/new primary malignancy

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: __ __ - __ __ __ - __ __ __ __
dd mmm yyyy

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: ____ ____ ____

EQ-5D Questionnaire

CCTG: BR.31

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

1. **Mobility**
   a. I have no problems in walking about ☐
   b. I have some problems in walking about ☐
   c. I am confined to bed ☐

2. **Self-Care**
   a. I have no problems with self-care ☐
   b. I have some problems washing or dressing myself ☐
   c. I am unable to wash or dress myself ☐

3. **Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
   a. I have no problems with performing my usual activities ☐
   b. I have some problems with performing my usual activities ☐
   c. I am unable to perform my usual activities ☐

4. **Pain/Discomfort**
   a. I have no pain or discomfort ☐
   b. I have moderate pain or discomfort ☐
   c. I have extreme pain or discomfort ☐

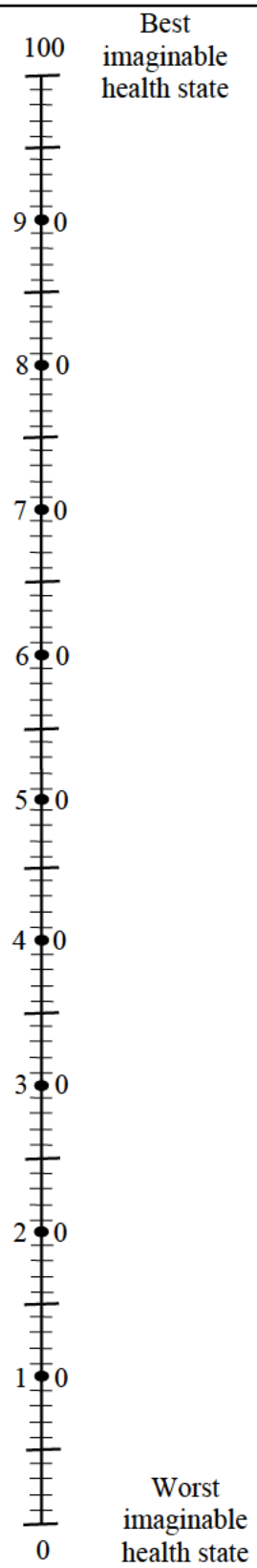
5. **Anxiety/Depression**
   a. I am not anxious or depressed ☐
   b. I am moderately anxious or depressed ☐
   c. I am extremely anxious or depressed ☐

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

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Please check to make sure you have answered all questions.

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

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

Thank you.

APPENDIX VIII - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

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

APPENDIX IX - BLINDING / UNBLINDING

Emergency Unblinding

MEDI4736 and matching placebo are identical in appearance as are the vials in which they are provided. Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's urgent management, the blind for that subject may be broken by the treating physician. Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding (i.e. almost all urgent situations can be managed by discontinuing study drug).

If a patient is unblinded, they are considered to be off MEDI4736/placebo treatment. Therefore the need to break the blind must first be discussed and approved by the CCTG. For any treatment code unblinding, the reason and parties involved must be documented in the patient's medical record. Treatment identification information should be kept confidential.

Please note: *Requests to unblind for information only or to permit participation in other clinical trials will not be considered until the trial has been unblinded and reported. However, in the event that it is necessary to determine whether a patient is an appropriate candidate to receive an approved standard of care therapy, then, on request of the treating physician, on a case-by-case basis, patients may be unblinded post-progression on BR.31.*

Unblinding Procedure:

To unblind the treatment for a patient you must contact CCTG and receive the approval from an CCTG Senior Investigator whenever possible.

8am-4pm (EST): Please send an email to the Study Coordinator or Senior Investigator including the trial code, patient identification, patient initials, last treatment kit (if applicable) and the reason for the unblinding request. Once approval is obtained from the Senior Investigator, authorized personnel at CCTG will unblind the patient and send the unblinding information via email to the Investigator who requested the unblinding.

(4pm-8am EST) and statutory holidays: Please phone the following number as appropriate:
North America calls: 833-896-9955Toll Free
International calls: 613-507-3861 (country code for Canada is "1")

You will be required to provide basic information regarding the trial code, patient identification, last treatment kit (if applicable), and the reason for the unblinding request as well as contact information of the caller (and the Investigator/treating physician to whom the information is to be relayed if different from the caller). The unblinding information will be conveyed to the Investigator by phone and may also be followed with a confirmation email or fax.

APPENDIX X - ROLE OF THE TRIAL AND DATA SAFETY MONITORING COMMITTEE

The Trials Committee:

Generally, trial committee members are drawn from their respective disease site committees. Trial committees are expected to

- Develop and write the trial protocol, with the assistance of central office;
- Make recommendations for modifications as necessary while the trial is in progress;
- Participate with central office and the Clinical Trials Committee in decisions regarding termination of the study; and,
- Write and submit the results of the study for publication.

The CCTG Standing Data Safety Monitoring Committee:

The CCTG has a single DSMC that is advisory to the Director, and responsible for assessing, at intervals, the progress of a clinical trial, safety data, and critical efficacy endpoints, and to recommend to the Director whether to continue, modify, or stop a trial. The DSMC is comprised of individuals who are both members and non – members of the CCTG; these individuals will be independent from those CCTG members responsible for carrying out the trials under consideration, including the faculty and staff of the CCTG Central Office.

The broad responsibilities of the DSMC of the CCTG are to assist in protecting the safety of trial participants and to facilitate meeting the mission of the CCTG which is "to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer with the ultimate goal of reducing morbidity and mortality from this disease". In order to meet this mission, the DSMC must assist in ensuring that the results of trials are valid and credible and that the continued conduct of a given trial will be consistent with this mission.

The responsibilities of the DSMC are to advise the CCTG on all matters related to the safety of subjects enrolled in its trials, and on selected matters related to the integrity and potential conclusions of study data and the appropriateness of continued trial conduct, including the results of interim analyses. All phase III trials, including this one, or subject to regular oversight by the DSMC

The recommendations of the DSMC and resulting actions will be communicated throughout the CCTG, including to the CTC, Disease Site Chairs, IND Program, Trial Study Chairs and Committees and membership.

For logistical reasons, the DSMC is kept small, while maintaining representation of all required skill areas and experience. Membership of the DSMC will include 9 – 14 individuals that ensure representation on the DSMC of the individuals with expertise or representation of the following categories:

i) systemic therapy of cancer (at least 2)
ii) radiation oncology (at least 2)
iii) surgical oncology (at least 1)
iv) biostatistics (at least 1)
v) clinical trials methodology (at least 1)

vi) ethics (at least 1)

vii) lay representative (at least 1)

viii) NCI US / CTEP representative (1)

ix) Non NCI US / CTEP cooperative group member external to CCTG

Members may be appointed on an ad hoc basis through a consultation process involving the DSMC Chair and the Director of the CCTG should additional expertise be required in the review of certain studies.

Preferences for Adjuvant Immunotherapy Questionnaire – ENGLISH

CCTG Trial: **BR.31**

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 patient preferences for adjuvant immunotherapy questionnaire: please check (✓)

☐ BASELINE

☐ POST TREATMENT (12 Weeks Post Treatment Visit, or if not conducted at this visit in error, completed as soon as possible afterwards)

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: __ __ - __ __ __ - __ __ __ __
dd mmm yyyy

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: ____ ____ ____

Preferences for adjuvant immunotherapy in non-small-cell lung cancer: what makes it worthwhile?

We would like to ask some general questions about you.

1. Roughly how many minutes does it take to travel from your home to this clinic? _____ *(please write number of minutes)*

2. If you were having immunotherapy, where would you be living during the time you were having it? *(please tick one)*

   At home ☐
   With relatives/ friends ☐
   Other ☐

3. What is the highest level of education you have completed? *(please tick one)*

   Primary *(or elementary)* school ☐
   High school prior to intermediate or school certificate *(some high school)* ☐
   Intermediate or school certificate *(high school completed)* ☐
   Trade or technical qualification ☐
   University or college degree ☐

4. How would you describe your employment in the year before your surgery? *(please tick one)*

   Employed full-time ☐
   Employed part-time/casual ☐
   Unemployed (not retired or on pension) ☐
   Retired or on pension ☐

5. What is your marital status? *(please tick one)*

   Married/ De facto ☐
   Separated / Divorced ☐
   Widowed ☐
   Single ☐

6. Do you have any children? Yes / No *(please circle one)*

7. Do you have any children who are dependent on your support? Yes / No *(please circle one)*

8. Do you have any people who are dependent on your support? Yes / No *(please circle one)*

9. Has a close friend or relative of yours died from cancer? Yes / No *(please circle one)*

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

10. How much of the time would relatives/friends be available to care for you if you needed it during the time you were having immunotherapy?

- None of the time ☐
- Some of the time ☐
- Most of the time ☐
- All of the time ☐

11. Which of the following best describes your use of tobacco (cigarettes, cigars or pipe)

- I have smoked within the last 1 month ☐
- I last smoked more than 1 month ago, but less than 12 months ago ☐
- I last smoked more than 12 months ago, but less than 10 years ago ☐
- I last smoked more than 10 years ago ☐
- I have never been a regular smoker (more than once a week for more than 1 year). ☐

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

The aim of this questionnaire is to find out how much of an improvement you think is needed to justify the side effects and inconvenience of adjuvant immunotherapy. Your opinion is important to us because of your personal experience with this situation. Your answers will be very helpful for people facing this decision in the future.

Everyone is given the same numbers and asked the same questions so that we can compare the answers.

The lengths of time and chances of reaching them are hypothetical. In other words, they are made up and do not apply to you personally.

Only the researchers involved in this study will see your answers.

We will write a report about this but won't include your name or personal details.

Please let us know if you have any questions or concerns.

Please imagine that there is a person your age sitting in the chair next to you.

Imagine that this person recently had surgery for lung cancer and is recovering well.

Imagine that the operation removed all the known cancer from their lung and lymph nodes, and that there are no signs that the cancer has spread to any other parts of their body.

This person understands, however, that there is still a chance that the cancer will come back.

This person now has to decide whether or not to have adjuvant immunotherapy**.**

Now let's imagine that this person can see into the future and knows exactly what will happen to them.

Suppose that this person knows

- exactly how long they will live for if they ***do not*** have adjuvant immunotherapy;
- exactly how long they will live for if they ***do*** have adjuvant immunotherapy; and,
- exactly what their experience of adjuvant immunotherapy will be like.

For example, suppose for the moment that this person knew that

- without adjuvant immunotherapy their life expectancy would be 5 years;
- with adjuvant immunotherapy, their life expectancy would also be 5 years; and,
- their experience of adjuvant immunotherapy would be exactly like yours.

In other words, having adjuvant immunotherapy would not provide any additional benefit and would not increase this person's life expectancy at all.

Please think for a moment about whether having adjuvant immunotherapy would be worthwhile in this situation, based on your knowledge of what adjuvant immunotherapy is like.

Now, let's suppose that this person knew that

- without adjuvant immunotherapy their life expectancy would be 5 years;
- with adjuvant immunotherapy their life expectancy would be 10 years; and,
- their experience of adjuvant immunotherapy would be exactly like yours.

In other words, having adjuvant immunotherapy would increase this person's life expectancy by 5 years.

Please think for a moment about whether having adjuvant immunotherapy would be worthwhile in this situation.

By asking you to make a series of choices like these with different numbers, we can work out the smallest improvement that you think would make the additional side effects and inconvenience of having adjuvant immunotherapy worthwhile.

In a moment, we'll ask you to put yourself in this person's position, that is,

- having to choose whether or not to have adjuvant immunotherapy;
- knowing what the life expectancy would be with and without adjuvant immunotherapy;
- knowing what you know about the side effects and inconvenience of adjuvant immunotherapy.

We tell everyone exactly the same story and use exactly the same numbers so that we can compare the answers. These numbers are hypothetical, imaginary, and do not apply to you personally.

There are four questions. Please answer them all.

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

Question 1

For each row, please tick only one box to show whether you would choose:

the *shorter* life expectancy *without* the side effects and inconvenience of adjuvant immunotherapy

OR

the *longer* life expectancy *with* the side effects and inconvenience of adjuvant immunotherapy.

"Immunotherapy" refers to 13 doses (over 1 year) of the immunotherapy that you were told about when you started this trial.

Answer these questions based on your knowledge of what having adjuvant immunotherapy is like.

In other words, consider what you have experienced, read or been told about its side effects and inconvenience.

***WITHOUT* immunotherapy your life expectancy is**				**_WITH_ immunotherapy your life expectancy is**
3 years	☐	OR	☐	3 years
3 years	☐	OR	☐	3 years and 1 month
3 years	☐	OR	☐	3 years and 3 months
3 years	☐	OR	☐	3 years and 6 months
3 years	☐	OR	☐	3 years and 9 months
3 years	☐	OR	☐	4 years
3 years	☐	OR	☐	4 ½ years
3 years	☐	OR	☐	5 years
3 years	☐	OR	☐	6 years
3 years	☐	OR	☐	8 years
3 years	☐	OR	☐	10 years
3 years	☐	OR	☐	13 years
3 years	☐	OR	☐	18 years

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

Question 2

For each row, please tick only one box to show whether you would choose:

the *shorter* life expectancy *without* the side effects and inconvenience of adjuvant immunotherapy

OR

the *longer* life expectancy *with* the side effects and inconvenience of adjuvant immunotherapy.

This question and the following two questions (Question 3 and Question 4) are talking about exactly the same type and length of immunotherapy as described in Question 1.

WITHOUT **immunotherapy your life expectancy is**				***WITH*** **immunotherapy your life expectancy is**
5 years	☐	OR	☐	5 years
5 years	☐	OR	☐	5 years and 1 month
5 years	☐	OR	☐	5 years and 3 months
5 years	☐	OR	☐	5 years and 6 months
5 years	☐	OR	☐	5 years and 9 months
5 years	☐	OR	☐	6 years
5 years	☐	OR	☐	6 ½ years
5 years	☐	OR	☐	7 years
5 years	☐	OR	☐	8 years
5 years	☐	OR	☐	10 years
5 years	☐	OR	☐	15 years
5 years	☐	OR	☐	20 years

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

Question 3

For each row, please tick only one box to show whether you would choose:

the *lower* chance of living 5 years *without* the side effects and inconvenience of adjuvant immunotherapy

OR

the *higher* chance of living 5 years *with* the side effects and inconvenience of adjuvant immunotherapy.

These questions are talking about exactly the same type and length of immunotherapy as Question 1.

***WITHOUT* immunotherapy your chance of living 5 years or more is**				**_WITH_ immunotherapy your chance of living 5 years or more is**
50%	☐	OR	☐	50%
50%	☐	OR	☐	51%
50%	☐	OR	☐	52%
50%	☐	OR	☐	53%
50%	☐	OR	☐	55%
50%	☐	OR	☐	60%
50%	☐	OR	☐	65%
50%	☐	OR	☐	70%
50%	☐	OR	☐	75%
50%	☐	OR	☐	80%
50%	☐	OR	☐	90%
50%	☐	OR	☐	100%

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

Question 4

For each row, please tick only one box to show whether you would choose:

the *lower* chance of living 5 years *without* the side effects and inconvenience of adjuvant immunotherapy

OR

the *higher* chance of living 5 years *with* the side effects and inconvenience of adjuvant immunotherapy.

These questions are talking about exactly the same type and length of immunotherapy as Question 1.

***WITHOUT* immunotherapy your chance of living 5 years or more is**				**_WITH_ immunotherapy your chance of living 5 years or more is**
65%	☐	OR	☐	65%
65%	☐	OR	☐	66%
65%	☐	OR	☐	67%
65%	☐	OR	☐	68%
65%	☐	OR	☐	70%
65%	☐	OR	☐	75%
65%	☐	OR	☐	80%
65%	☐	OR	☐	85%
65%	☐	OR	☐	90%
65%	☐	OR	☐	95%
65%	☐	OR	☐	100%

Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____
Today's date (Year, Month, Day): _____

Thank you.

APPENDIX XII - IMAGING AND VISIT SCHEDULE

The schedule below outlines the post-randomization visit and imaging required for a BR.31 patient who receives all protocol treatment and does not have a disease event until at least 5 years after randomization.

Weeks / Months from Randomization	Infusion delivered	CT scan	Visit	Folder for EDC entry
Week 0	X [1]		X	Treatment Report #1
Week 4	X		X	Treatment Report #2
Week 8	X		X	Treatment Report #3
Week 12	X	X	X	Treatment Report #4
Week 16	X		X	Treatment Report #5
Week 20	X		X	Treatment Report #6
Week 24	X	X	X	Treatment Report #7
Week 28	X		X	Treatment Report #8
Week 32	X		X	Treatment Report #9
Week 36	X	X	X	Treatment Report #10
Week 40	X		X	Treatment Report #11
Week 44	X		X	Treatment Report #12
Week 48	X	X	X	Treatment Report #13
Week 52			X [2]	12 Week Follow Up Report (or Treatment Report #13 if visit must be completed early)
Week 56				12 Week Follow Up Report
Week 60		X	X [3]	
Week 64				Follow-up Report #1
Week 68				
Week 72		X	X	
Week 76				Follow-up Report #2
Week 80				
Week 84		X	X	
Week 88				Follow-up Report #3
Week 92				
Week 96		X	X	
Week 100				Follow-up Report #4
Week 104				
Week 108		X	X	
Month 27				Follow-up Report #5
Month 30		X	X	
Month 33				Follow-up Report #6
Month 36		X	X	
Month 39				Follow-up Report #7
Month 42				
Month 45				
Month 48		X	X	
Month 51				Follow-up Report #8
Month 54				
Month 57				
Month 60		X	X	

1 Must be administered within 2 days of randomization.
2 To be done 28 days after the day of the last treatment infusion.
3 To be done 12 weeks from the date of last infusion.

Note: Annual imaging and visit schedule continues until death or disease event, whichever is first. See section 9 for details.

This schedule was developed to synchronize clinic visits with protocol-required imaging to minimize inconvenience for patients. Regardless of deviations from the clinic visit schedule, the imaging schedule outlined above and in Sections 9.1 and 9.2 must be maintained. If a deviation from the imaging schedule occurs, all attempts must be made to undertake the required imaging as soon as possible then patient must return to the original imaging schedule.

Patients that stop protocol therapy prior to completion of the full year of treatment for reasons other than a disease event must follow the imaging and visit schedules outlined in Section 9.2 even though, in some cases, this may result in imaging that is not synchronized with clinic visits.

APPENDIX XIII - 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) 28Oct2022 Version

Toxicity Management Guidelines (TMGs)

Drug Substance	Durvalumab and Tremelimumab
TMG Version	28 October 2022

ANNEX TO PROTOCOL

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Note: Annex is to be used in any clinical trial protocol within which patients are treated with Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Table of Contents

VERSION HISTORY

October 2022

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either durvalumab or tremelimumab or a combination of these two immune checkpoint inhibitors (ICI) is used in combination with other anti-cancer drugs (e.g., antineoplastic chemotherapy, targeted agents). These other anticancer drugs can be administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination ICI regimens, with specific instructions for ICI dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and non-immune–mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in clinical study protocol (CSP) – whether that is durvalumab alone, tremelimumab alone, or durvalumab + tremelimumab in combination, or durvalumab +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to CSP, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. TMG updates are iterated by date, and should be used in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version specified in the CSP.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy –October 2022

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.

Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider the need for glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- **Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation**
- **Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy**
- **Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .**

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435
2. Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36(17):1714-1768.
3. Haanen JBAG, et al. Management of toxicities for immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2017;28(Suppl4):i119-i1142.

4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320-341.

5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 1.2022. Published February 28, 2022.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	− All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. − The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. − The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients. − The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. − For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. − With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease). – Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (CT) scan. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of	**For Grade 2** – Monitor symptoms daily and consider hospitalization, as clinically indicated. – Consider Pulmonary and Infectious Diseases Consults; – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent).

		steroid taper (≤10 mg prednisone or equivalent).	– Consider HRCT or chest CT with contrast, Repeat imaging study as clinically indicated – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider, discussing with Clinical Study Lead.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Hospitalize the patient – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression,

	study protocol for defining the CTCAE grade/severity)		other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity improves to Grade ≤1, then study drug/study regimen can be	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

		resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	(e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. − Consider further evaluation with imaging study with contrast. − Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.** − **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** − Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** − For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (≤10 mg prednisone per day, or equivalent). − For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study	**For Grade 3 or 4** − Urgent GI consult and imaging and/or colonoscopy as appropriate. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − Monitor stool frequency and volume and maintain hydration. − If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		investigator, in discussion with AstraZeneca Clinical Study Lead. **<u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy,</u>** **Permanently discontinue both durvalumab and tremelimumab for** **1) Grade 3 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis ***Infliximab should not be used for management of immune-related hepatitis.*** **PLEASE SEE shaded area immediately below this management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin .
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	– No dose modifications. – If it worsens, then consider holding therapy.	– Continue transaminase and total bilirubin monitoring per protocol.
	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	– Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). – Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3 × ULN AND	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.

		bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	– If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5- ≤ 10 x ULN	– Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). – **If in combination with tremelimumab, do not restart tremelimumab.**	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – Perform Hepatology Consult, abdominal workup, and imaging as appropriate. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis (elevated transaminases and total bilirubin) ***Infliximab should not be used for management of immune-related hepatitis.***	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg).

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])			– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	Isolated AST or ALT >ULN and ≤2.5×BLV,	– No dose modifications. – If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. – For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	ALT or AST > 2.5- ⩽ 5X BLV and ⩽ 20xULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5×BLV . – If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5×BLV , resume study drug/study regimen after completion	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead.

	of steroid taper (<10 mg prednisone, or equivalent).	– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN	– Withhold durvalumab and permanently discontinue tremelimumab – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue study drug/study regimen.	**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider Consulting a nephrologist. – Consider imaging studies to rule out any alternative etiology – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). Follow urine protein/creatinine ratio every 3-7 days
	Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. – Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion	**For Grade 2** – Consider including hydration, electrolyte replacement, and diuretics as clinically indicated – Follow urine protein/creatinine ratio every 3-7 days – Carefully monitor serum creatinine as clinically warranted.

		of steroid taper (<10 mg prednisone, or equivalent).	− Consult nephrologist and consider renal biopsy if clinically indicated. − Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out − If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** − Carefully monitor serum creatinine daily. − Follow urine protein/creatinine ratio every 3-7 days − Consult nephrologist and consider renal biopsy if clinically indicated. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3 to 5 days of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant
Rash or Dermatitis **(Including Pemphigoid)**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology. − Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.**

			– **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**For Grade 3** – Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 4** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

			− Consider hospitalization. − Monitor the extent of rash [Rule of Nines]. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). − Consider consulting an endocrinologist for endocrine events. − Consider discussing with Clinical Study Lead, as needed. − Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. − Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide

			assessment of early morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	– For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve. – Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression,

	study protocol for defining the CTCAE grade/severity)		viral infection, concomitant medications, substance abuse). − For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. − Assess for signs/symptoms of pancreatitis − Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) − If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase − If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology. − Consider Gastroenterology referral
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** − Consider IV hydration − Consider Gastroenterology referral

	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study regimen	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available – Consider, as necessary, discussing with Clinical Study Lead.(Last bullet) – Consider hospitalization.

			– Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. –	**For Any Grade** – Consider neurology consult – Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. – Exclude bacterial and viral infections. (i.e. HSV)Consider IV acyclovir until polymerase chain reactions are available.
	Grade 2	**For Grade 2** Permanently discontinue study drug/study regimen.	**For Grade 2** – Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisolone 1–2 mg/kg/day – For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis
Transverse Myelitis	**Any Grade**	**General Guidance** – Permanently discontinue immunotherapy – Consider MRI of the spine and brain	**For Any Grade** – Consider neurology consult – Inpatient care – Consider prompt initiation of high methylprednisolone pulse dosing – Strongly consider IVIG or plasmapheresis

		− Once imaging is complete, consider lumbar puncture Consider testing to rule out additional aetiologies: B12, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel for anti-Hu and anti-CRMP5/CV2	
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. − Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modifications.	**For Grade 1** − Consider discussing with the Clinical Study Lead, as needed. − Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2** − Consult a neurologist. − Consider EMG/NCS

			− Consider discussing with the Clinical Study Lead, as needed. − Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally − If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** − Consider discussing with Clinical Study Lead, as needed. − Recommend hospitalization. − Monitor symptoms and consult a neurologist. − **Treat per Guillain-Barré Syndrome recommendations**
Guillain-Barré Syndrome (GBS)		General Guidance	− Recommend hospitalization − Obtain neurology consult − Obtain MRI of spine to rule out compression lesion − Obtain lumbar puncture − Antibody tests for GBS variants − Pulmonary function tests − Obtain electromyography (EMG) and nerve conduction studies − Frequently monitor pulmonary function tests and neurologic evaluations − Monitor for concurrent autonomic dysfunction − Initiate medication as needed for neuropathic pain
	Grade 2-4	Grade 2-4 Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		General Guidance	− Obtain neurology consult − Recommend hospitalization − Obtain pulmonary function tests

			− Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies − Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis − Obtain electromyography (EMG) and nerve conduction studies − Consider MRI of brain/spine to rule out CNS involvement by disease − Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)
	Grade 2	Permanently discontinue	− Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) − Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	Permanently discontinue	− Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement − Start plasmapheresis or IVIG − Consider rituximab if refractory to plasmapheresis or IVIG − Frequent PFT assessments − Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** − Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with

			baseline cardiopulmonary disease and reduced cardiac function. − Consider discussing with the Clinical Study Lead, as needed. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	− If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** − Monitor symptoms daily, hospitalize. − Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy − Supportive care (e.g., oxygen). − If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

	defining the CTCAE grade/severity)		− Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, and; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. − If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. − Consider, as necessary, discussing with the Clinical Study Lead. − Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
	Grade 1	− No dose modifications.	**For Grade 1** − Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. − Consider Neurology consult.

		– Consider, as necessary, discussing with the Clinical Study Lead.
Grade 2	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider additional – immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3	**For Grade 3** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30	**For Grade 3** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.

		days or if there are signs of respiratory insufficiency.	– If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**Grade 4** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

[1] SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	– Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** − The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. − Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard or study protocol prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** − Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

List of Abbreviations

AChE	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotropic hormone	imAE(s)	Immune-mediated adverse event(s)
ALT	Alanine aminotransferase	INR	International normalized ratio
ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CSP	Clinical Study Protocol	MRCP	Magnetic resonance cholangiopancreatography
CT	Computed tomography	MRI	Magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events	NCCN	National Comprehensive Cancer Network
CTLA-4	Cytotoxic T-lymphocyte antigen-4	NCI	National Cancer Institute
DILI	Drug-induced liver injury	PD-L1	Programmed cell death ligand-1
ECG	Electrocardiogram	PJP	Pneumocystis jirovecii pneumonia
ECHO	Echocardiogram	PO	By mouth
ESMO	European Society of Medical Oncology	SCAR	Severe cutaneous adverse reaction
GI	Gastrointestinal	SITC	Society for Immunotherapy of Cancer
HBcAb	Hepatitis B core antibody	SJS	Stephen Johnson Syndrome
HBeAg	Hepatitis B envelope antigen	T1DM	Type 1 diabetes mellitus
HBsAg	Hepatitis B surface antigen	T3	Triiodothyronine
HBV	Hepatitis B virus	T4	Thyroxine
HCC	Hepatocellular cancer	TEN	Toxic Epidermal Necrolysis
HCV	Hepatitis C virus	TMG(s)	Toxicity management guideline(s)
HgA1c	Hemoglobin A1C	TSH	Thyroid stimulating hormone
ICI(s)	Immune checkpoint inhibitor(s)	ULN	Upper limit of normal

APPENDIX XIV- COVID-19 AND EMERGENCY SITUATIONS AND COMPLIANCE

1.0 Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol 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 or within 4 weeks of a significant protocol milestone (e.g. declaration of clinical cut-off date for interim or final analyses, etc.), 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.

2.0 Remote Monitoring/Auditing

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

The above mentioned documentation 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.

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)	Carolyn Wilson Study Coordinator CCTG Email: cwilson@ctg.queensu.ca	613-533-6430	613-533-2941
	or: Dr. Chris O'Callaghan Senior Investigator, CCTG Email: cocallaghan@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Glenwood Goss Study Chair Email: ggoss@toh.on.ca		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Chris O'Callaghan Senior Investigator, CCTGs or: Carolyn Wilson Study Coordinator, CCTG Email: cwilson@ctg.queensu.ca	613-533-6430	613-533-2941
DRUG SUPPLY See Appendix III for full details.	Web based ordering [MANGO] will be used. Full details and toll-free numbers will be supplied at study activation		
REQUESTS FOR UNBLINDING	During office hours (8 am-4 pm EST): Constance Laroche-Lefebvre Study Coordinator, CCTG Email: claroche-lefebvre@ctg.queensu.ca or: Dr. Chris O'Callaghan Senior Investigator, CCTG Email: cocallaghan@ctg.queensu.ca	613-533-6430	613-533-2941
	After office hours (4 pm- 8 am EST): North American calls (toll free): 833-896-9955 International calls: 613-507-3861 (country code for Canada is "1")		