PrECOG Protocol Number: PrE0505

Open Label, Phase II Study of Anti - Programmed Death – Ligand 1 Antibody, Durvalumab (MEDI4736), in Combination with Chemotherapy for the First-Line Treatment of Unresectable Mesothelioma

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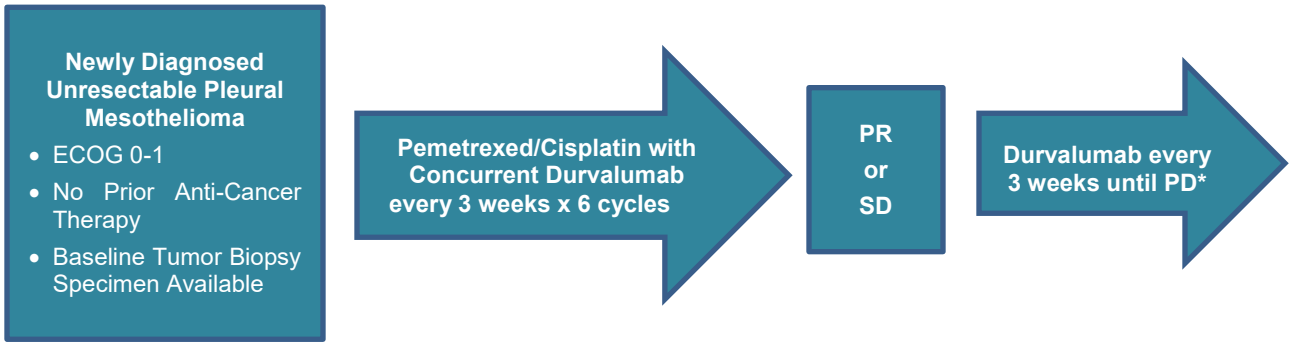
Brief Protocol Synopsis

See Protocol Document Sections for complete details

This is a single arm, open label phase II study of the anti-PD-L1 antibody, durvalumab, in combination with pemetrexed and cisplatin chemotherapy in the first-line treatment of patients with unresectable pleural mesothelioma. Standard chemotherapy with pemetrexed/cisplatin will be given for up to six 3-week cycles with the addition of concurrent durvalumab dosed at 1120 mg every 3 weeks. The first 6 patients who are enrolled and commence treatment will be monitored for safety of the combination. Use of carboplatin in place of cisplatin will be permitted for patients who are ineligible for cisplatin due to a documented contraindication (e.g., ototoxicity, renal function), however these patients must otherwise fulfill the eligibility criteria for the study. For patients who receive cisplatin, carboplatin may also be substituted after Cycle 1 for cisplatin related toxicity (e.g., grade 3 ototoxicity, grade 3 nausea) at the investigator's discretion. After completion of Cycle 6 of concurrent therapy, patients with stable or responding disease per modified RECIST for malignant mesothelioma will continue on single agent durvalumab 1120 mg every 3 weeks until progression. Maximum duration of durvalumab treatment is 12 months starting from Cycle 1 of concurrent treatment (inclusive of any treatment delays or missed treatments).

The primary endpoint of the study is overall survival (OS) as compared with historical control.

Study Schema



Treatment should begin within 10 working days of registration.

PR: Partial Response; **SD:** Stable Disease; **PD:** Progression

***** Maximum duration of durvalumab treatment is 12 months starting from Cycle 1 of concurrent treatment.

Accrual: This study will enroll 55 patients (of whom 50 will be expected to be eligible and commence treatment). The first 6 patients who are enrolled and commence treatment will be monitored for safety of the combination, safety will be further evaluated after 15 patients have been enrolled.

NOTE: Carboplatin may be substituted for cisplatin as indicated in Section 3.9 and Section 5.1.

List of Abbreviations

Abbreviation	Term
AChE	Acetylcholine Esterase
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
Anti-HBc	Hepatitis B Core Antibody
AR	Accumulation Ratio
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
BID	Twice a Day
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CD	Cluster of Differentiation
CDC	Complement Dependent Cytotoxicity
CI	Confidence Interval
CL	Clearance
C_{max}	Peak Concentration
CR	Complete Response
CNS	Central Nervous System
CrCl	Creatinine Clearance
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen 4
DCO	Data Cut-Off
DCR	Disease Control Rate
dL	Deciliter
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid

DOR	Duration of Response
EA CBPF	ECOG-ACRIN Central Biorepository and Pathology Facility
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EDTA	Disodium Edetate Dihydrate
ELISA	Enzyme-Linked Immunosorbent Assay
F	Fahrenheit
Fcγ	Fragment Crystallizable Gamma
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
g	grams
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-γ	Interferon Gamma
IG	Immunoglobulin
IgG1κ	Immunoglobulin G1 Kappa
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
imAE	Immune-Mediated Adverse Event
IRB	Institutional Review Board

IV	Intravenous(ly)
IVIG	Intravenous Immunoglobulin
kDa	Kilodalton
kg	Kilogram
LFT	Liver Function Test
LLN	Lower Limit of Normal
MAb	Monoclonal Antibody
mCR	Marrow Complete Remission
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
m^2	Square Meter
mm^3	Cubic Millimeter
MRI	Magnetic Resonance Imaging
ms	Milliseconds
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-Observed-Adverse-Effect Level
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PJP	Pneumocystis Jirovecii Pneumonia
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PO	Oral
PPD	Purified Protein Derivative
PR	Partial Response
PT	Prothrombin Time

Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q4W	Every 4 Weeks
QTc	The Time Between the Start of the Q wave and the End of the T Wave Corrected for Heart Rate
QTcF	QT Interval on ECG Corrected using the Frederica's Formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
sPD-L1	Soluble Programmed Cell Death Ligand 1
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-Life
TBD	To Be Determined
TBSA	Total Body Surface Area
T-Cell	T Lymphocyte
TNBC	Triple-Negative Breast Cancer
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor- Alpha
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
W/V	Weight/Volume

1. Introduction- Background and Rationale

1.1 Mesothelioma – Disease Overview

Mesothelioma is a malignant tumor of mesothelial surfaces primarily arising in the thoracic pleura and is estimated to cause 43,000 deaths worldwide each year with over 3300 cases occurring annually in the United States [1, 2]. Approximately 80% of cases of mesothelioma are due to inflammation induced by prior asbestos exposure with a lead time from exposure to development of cancer of 20-30 years [1]. It is predicted that the incidence of mesothelioma due to previous exposure will rise significantly in many countries over the next two decades particularly in Europe, China, Russia and Japan [3, 4]. The median survival for all patients diagnosed with mesothelioma is extremely poor at 6-18 months and the vast majority of patients will relapse after surgical resection or present with unresectable disease [5, 6]. The known role of asbestos and chronic inflammation in the etiology of mesothelioma has led to the discovery of the pivotal role the immune system plays in the initiation and progression of mesothelioma [7]. Immunotherapy is one of the most promising avenues of clinical investigation in mesothelioma at present and several clinical trials are evaluating immune modulating agents [8].

1.2 Background/Rationale

1.2.1 PD-L1 in Immune Evasion

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung [9], renal [10, 11, 12], pancreatic [13, 14, 15], ovarian cancer [16], and hematologic malignancies [17, 18] tumor cell expression of PD-L1 is associated with reduced survival and an unfavourable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell [19, 20]. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination [21].

1.2.2 PD-L1 is Highly Expressed in Mesothelioma

Preclinical data suggests that one of two ligands of PD-1, programmed death-ligand 1 (PD-L1) is highly expressed in mesothelioma tumor cells [22]. PD-L1 is a putative predictive marker for response to PD-L1- and PD-1-directed therapeutics in multiple tumor types across multiple early and late phase studies [23-25].

We have recently performed PD-L1 immunohistochemical (IHC) testing, using the murine anti-human PD-L1 monoclonal antibody 5H1, on standard formalin-fixed paraffin-embedded (FFPE) tissue sections of large biopsy or resection specimens from 25 pleural (17 epithelioid, 7 biphasic & 1 sarcomatoid) and 8 peritoneal mesotheliomas. Based on earlier published studies tumor cells or tumor infiltrating

lymphocytes were considered positive if at least 5% exhibited membranous staining [23]. The mesothelioma tumor cells in the analyzed cohort demonstrated high levels of PD-L1 expression, 17 of 33 tumors (52%) were PD-L1 positive and high level expression (>50% staining) was present in 14 of 33 tumors (42%). Another group has recently reported similar findings from 224 patient cases analyzed retrospectively using the 5H1 antibody [26]. Using a 5% cutoff for positivity, 40% of mesothelioma tumors expressed PD-L1 (89/224). PD-L1 expression was associated with worse overall survival (6 months vs. 14 months, $p<0.0001$) even when adjusted for age, gender, lymphocytic infiltration and therapeutic surgery ($p<0.0002$).

Recent analysis of gene expression suggests high levels of CD8 infiltration in 32% of mesotheliomas and high level PD-L1 expression in 12 of 44 tumors (27%) providing a further rationale for PD1/PD-L1-directed therapy in mesothelioma [27].

In addition recent data from a mesothelioma cohort enrolled in a phase Ib clinical trial of the anti-PD-1 antibody, pembrolizumab, were highly promising with 28% (7/25) of chemo-refractory patients have an objective response by modified Response Evaluation Criteria in Solid Tumors (RECIST) for mesothelioma and a further 48% (12/25) having prolonged stable disease [28]. This has led to a phase II single arm clinical trial of pembrolizumab in the second- and third-line setting [29].

1.3 Study Drug - Durvalumab [30]

1.3.1 Description of Durvalumab (MEDI4736)

Durvalumab is briefly described below. Investigators should refer to the current Investigator's Brochure (IB) for details.

1.3.2 Product Derivation

Durvalumab is being developed as a potential anticancer therapy for the treatment of multiple tumor types. Durvalumab is a human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (MAb) that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T-lymphocyte (T-cell) and, cluster of differentiation on CD80 (B7-1) on immune cells and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).

1.3.3 Non Clinical Safety Profile

The non-clinical experience is fully described in the current version of the durvalumab IB.

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80 (B7-1).

[redacted]

1.3.4 Summary of Clinical Experience

The clinical experience is fully described in the current version of the durvalumab IB.

As of 12 July 2017, an estimated 4067 patients have been exposed to 1 or more doses of durvalumab in Phase I-III AstraZeneca or MedImmune sponsored studies, either as monotherapy or in combination and 5911 where the treatment arm is blinded. Additionally, more than 4000 patients have been exposed to 1 or more doses of durvalumab in externally-sponsored/investigator-initiated clinical trials. No AstraZeneca or MedImmune study has been terminated prematurely due to toxicity.

1.3.5 Clinical Pharmacology

1.3.5.1 Pharmacokinetics and Metabolism of Durvalumab in Humans

[redacted]

1.3.6 Clinical Safety & Preliminary Clinical Efficacy

1.3.6.1 Study CD-ON-MEDI4736-1108

Adverse Events (AEs)

[redacted]

Preliminary Efficacy

Study CD-ON-MEDI4736-1108:

- [redacted]

[redacted]

1.3.6.2 Study D4190C00007

[redacted]

AEs

[redacted]

SAEs

[redacted]

Preliminary Efficacy

[redacted]

NOTE: Further detailed information on adverse events and preliminary efficacy noted in clinical studies of durvalumab is available in the IB.

1.3.7 Dose Rationale

1.3.7.1 Fixed Dosing

A two compartment population PK model was developed for durvalumab using monotherapy data from Study CD-ON-MEDI4736-1108 and the ATLANTIC Study across dose levels and tumor types [redacted].

Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposure ($AUC_{ss,0-28}$, $C_{max,ss}$, and $C_{min,ss}$) using the population PK model. A fixed dose of 750 mg Q2W was selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40–110 kg. Simulation results demonstrate that body weight-based (10 mg/kg Q2W) and fixed dosing regimens (750 mg Q2W) yield similar median steady state exposures and associated variability, supporting the potential switch of durvalumab from weight-based to fixed dose. Similar considerations hold for the Q4W dosing regimens (20 mg/kg Q4W versus 1500 mg Q4W). Based on an average body weight of 75 kg, fixed doses of 1120 mg q3w (equivalent to 15 mg/kg q3w) of durvalumab are chosen for this study.

Similar findings have been reported by others [31-35]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies [32]. In addition, they investigated 18 therapeutic proteins and peptides.

1.4 Study Drugs – Pemetrexed and Cisplatin or Carboplatin

1.4.1 Pemetrexed

Pemetrexed is a folate analog metabolic inhibitor indicated for the treatment of mesothelioma in combination with cisplatin. Pemetrexed is administered intravenously at a dose of 500 mg/m² on Day 1 of each 21-day cycle. Cisplatin should be administered 30 minutes after pemetrexed infusion ends at a dose of 75 mg/m². The premedication regimen for pemetrexed includes folic acid and vitamin B12 as well as dexamethasone or equivalent to reduce cutaneous reactions. Subjects receiving pemetrexed should be monitored prior to each dose using complete blood count (CBC) and renal function tests. If marrow suppression is noted, dose modifications are noted in Section 6.3.2, Table 6-3. For renal toxicity, pemetrexed should be held when the creatinine clearance (CrCl) <45 mL/minute. Caution should be used among subjects who are receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and who have mild to moderate renal insufficiency (CrCl between 45 and 79 mL/minute). Caution should also be used when nephrotoxic drugs are administered with pemetrexed. For preparation and storage, please consult the prescribing information for Alimta® [36].

1.4.2 Cisplatin

Cisplatin is a platinum-based drug that is used in mesothelioma. Cisplatin is administered intravenously at a dose of 75 mg/m² starting 30 minutes after pemetrexed infusion ends. Subjects who are receiving cisplatin must be monitored for nephrotoxicity, ototoxicity and neuropathy in addition to myelosuppression. Caution must be observed in the case of nausea, vomiting and dehydration. Dose modifications according to toxicities are noted in Section 6.3.2, Table 6-3. For preparation and storage, please consult the prescribing information for Cisplatin [37].

1.4.3 Carboplatin

Carboplatin is a platinum-based drug that is used in the treatment of mesothelioma in the setting where cisplatin is contraindicated. Carboplatin is administered intravenously at a dose of AUC 5 mg/mL*min (per Calvert formula) starting 15 to 30 minutes after pemetrexed infusion ends. Subjects who are receiving carboplatin must be monitored for myelosuppression and anaphylaxis. Dose modifications according to toxicities are noted in Section 6.3.2, Table 6-3. For preparation and storage, please consult the prescribing information for Paraplatin [38].

1.5 Summary of Rationale for Proposed Study

1.5.1 Rationale for the Study Design and Treatment Plan

1.5.1.1 Current Standard of Care in Mesothelioma and Role for Maintenance Therapy

Subjects enrolled on this study will have unresectable mesothelioma for which they have not received prior systemic therapy. The standard first-line therapy for mesothelioma consists of 4-6 cycles of combination chemotherapy with pemetrexed/cisplatin, this has been shown to extend survival when compared with cisplatin alone and is associated with a median OS of 12.1 months [39]. The benefit of second-line chemotherapy has not been clearly established [40].

No more than 4 to 6 cycles of first-line platinum-based combination chemotherapy are generally recommended for patients with advanced disease. Therefore, after 4 to 6 cycles of treatment, non-progressing patients enter a “watch-and-wait” period with periodic review until progression. Trials are ongoing evaluating the role of maintenance single agent pemetrexed after initial platinum doublet chemotherapy [41]. Further investigation would be advantageous to provide these patients with a regimen that could augment and then maintain the disease control achieved by first-line therapy. Similar approaches in NSCLC have led to the approval of both erlotinib and pemetrexed as maintenance treatment in patients who are not progressing following first-line platinum-based treatment, on the basis of an observed benefit in both median progression-free survival (PFS) and median OS. Currently there are no approved therapies following first-line treatment for malignant pleural mesothelioma, and there are limited data in the maintenance setting.

1.5.1.2 Rationale for Combination of Chemotherapy and Durvalumab

The interaction of a tumor with the immune system is complex. Tumors and the tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor.

Cancer therapeutics such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

In previously untreated mesothelioma, chemotherapy has the potential to prime the immune system through tumor destruction and consequent antigen expression. The addition of durvalumab to chemotherapy is expected to be synergistic in this regard. Several studies are exploring the combination of chemotherapy with anti-PD-L1 therapies with promising early response data.

1.6 Synopsis of Study Design

1.6.1 Initial Enrollment and Evaluation for Safety (Safety Run-In Period)

As durvalumab has not been previously combined with pemetrexed platinum doublet chemotherapy the study will commence with an initial enrollment of 6 patients who will receive the combination of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) with durvalumab (1120 mg) for up to 6 cycles. Pemetrexed/carboplatin is associated with fewer toxicities than pemetrexed/cisplatin therefore both in the initial 6 patient cohort and in the later expansion, substitution of carboplatin (AUC 5) for cisplatin will be permitted specifically as outlined in the eligibility. After up to 6 cycles of concurrent chemotherapy with durvalumab, patients who have a PR or SD will continue on durvalumab until disease progression (maximum duration of durvalumab treatment is 12 months starting from Cycle 1 of concurrent treatment (inclusive of any treatment delays or missed treatments). In this initial safety run-in period subjects will be monitored for safety. The combination will be declared intolerable if ≥ 2 of the initial 6 patients experience a dose-limiting toxicity (DLT) as defined in the protocol and occurring during the first 2 cycles of concurrent therapy. The detailed statistical analysis plan is described in the statistical section of this protocol.

1.6.2 Expansion

After the initial 6 patients from the above safety run-in period have been monitored for safety the study will proceed with enrollment for a total of 55 patients (including the initial 6 patient safety run-in) of whom it is expected 50 patients will receive treatment (ineligibility rate of 10%). This is an open label, single arm phase II study evaluating the benefit of durvalumab in combination with pemetrexed/cisplatin for the treatment of first-line unresectable pleural mesothelioma. Durvalumab (1120 mg q 3 weeks) will be administered concurrently with up to 6 cycles of first line pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) followed by maintenance durvalumab until disease progression (maximum duration of durvalumab treatment is 12 months starting from Cycle 1 of concurrent treatment (inclusive of any treatment delays or missed treatments). Carboplatin (AUC 5) may be substituted for cisplatin for patients with a documented contraindication (e.g., ototoxicity, renal function) to use of cisplatin and these patients must otherwise fulfill the eligibility criteria (Section 3). In addition, for patients who receive cisplatin, carboplatin may be substituted after Cycle 1 for cisplatin related toxicity (e.g., grade 3 ototoxicity, grade 3 nausea) at the investigator's discretion.

1.6.3 Evaluation of Subjects

Progression will be assessed locally using modified RECIST Version 1.1. Subjects will continue to receive treatment until disease progression or other discontinuation criteria are met (maximum duration of durvalumab treatment is 12 months starting from Cycle 1 of concurrent treatment (inclusive of any treatment delays or missed treatments). Removal of subjects for clinical progression will be at the discretion of the Investigator. Response assessments will be performed every 6 weeks (2 doses of treatment) for the first 18 weeks. After 18 weeks of treatment, response assessments will be performed every 9 weeks (3 doses of treatment). The same method of assessment should be used throughout the study.

Following documentation of non-fatal confirmed disease progression, all subjects will be followed for survival (either routine clinic visit or telephone contact) every 3 months until death or the closure of the study.

2. Study Objectives

2.1 Primary Objective

The primary objective of this phase II study is to demonstrate improved overall survival (OS) compared to a historic control with the addition of concurrent and maintenance durvalumab to standard chemotherapy for unresectable pleural mesothelioma.

2.2 Secondary Objectives

1) To evaluate the safety and tolerability of durvalumab and durvalumab in combination with chemotherapy in subjects with malignant pleural mesothelioma.
2) Percentage of patients progression-free at 24 weeks from the time of registration. Disease status at 24 weeks will be compared to disease status at the time of registration, and response coded based on modified RECIST 1.1 criteria.
3) Progression-free survival (PFS) will be measured from the time of study registration until radiologic progression, clinical progression or death.
4) Time to progression on durvalumab will be measured from the time concurrent treatment with chemotherapy/durvalumab begins until radiologic or clinical progression is noted.
5) Best Objective Response Rate (ORR) evaluation will continue up to 1 year on therapy and response will be coded based on modified RECIST Version 1.1 criteria for mesothelioma.

2.3 Exploratory Objectives

2.3.1 Laboratory Correlates of Response (depending on sample availability)

1) Assessment of tumor baseline PD-L1 expression may be performed.
2) Assessment of the genomic and neoantigen landscape of baseline tumors may be performed.
3) Assessment of dynamics of circulating cell free tumor DNA (ctDNA) may be performed.
4) Serial assessment of soluble biomarkers may be performed.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

PrECOG Patient No. _____

Patient's Initials (F, M, L) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the Medical Monitor or Study Site Contact.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

_____ 3.1. Histologically and/or cytologically confirmed malignant pleural mesothelioma (any histologic subtype of malignant pleural mesothelioma is permitted).

Date of Diagnosis: _____

_____ 3.2 Unresectable disease (defined as the participant not being a candidate for curative surgery).

_____ 3.3 *Measurable disease, defined as at least 1 lesion (measurable) that can be accurately* assessed at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for repeated assessment (modified RECIST for pleural mesothelioma).

_____ 3.4 Available unstained archived tumor tissue sample in sufficient quantity to allow for analyses. At least fifteen unstained slides or a tumor block (preferred).

NOTE: A fine needle aspiration sample is not sufficient to make the patient eligible for enrollment. Given the complexity of mesothelioma pathological diagnosis and that these will be newly diagnosed patients it is expected that they will have a core needle biopsy or surgical tumor biopsy as part of their initial diagnostic work up.

_____ 3.5 Age ≥ 18 years.

_____ 3.6 ECOG performance status of 0-1 (Appendix I).

_____ 3.7 Ability to understand and willingness to sign IRB-approved informed consent.

_____ 3.8 Willing to provide archived tumor tissue and blood samples for research (Section 13.0).

_____ 3.9 Adequate organ function as measured by the following criteria, obtained ≤ 2 weeks prior to registration:

- Absolute Neutrophil Count (ANC) ≥ 1500/mm^3

  ANC: _____ Date of Test: _____

- Hemoglobin >9.0 g/dL

  Hemoglobin: _____ Date of Test: _____

- Platelets >100,000/mm^3

  Platelets: _____ Date of Test: _____

- Serum creatinine CL>60 mL/min by the Cockcroft-Gault formula (Appendix II) or by 24-hour urine collection for determination of creatinine clearance:

  Creatinine Clearance: _____ Date of Test: _____

  NOTE: Patients with a creatinine Cl ≥ 45 mL/min however ≤ 60 mL/min may be considered for enrollment provided they fulfill all other eligibility criteria, these subjects will receive pemetrexed/**carboplatin** concurrent with durvalumab during the combination phase of treatment. Patients with a creatinine CL<45 mL/min should not be enrolled.

- Albumin ≥ 2.8 g/dL

  Albumin: _____ Date of Test: _____

- Total Bilirubin ≤ 1.5x ULN [This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed to enroll only in consultation with their physician.]

  Total Bilirubin: _____ ULN: _____ Date of Test: _____

- AST/ALT ≤ 2.5x ULN (≤ 5x ULN in patients with liver metastases)

  AST/ALT: _____ ULN: _____ Date of Test: _____

_____ 3.10 Women must either be of non-reproductive potential (i.e., post-menopausal by history: ≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

Is the patient a woman of childbearing potential? _____ (yes/no)

If yes, Date of Test: _____ Results: _____

_____ 3.11 Women must not be pregnant or breastfeeding. Females of child-bearing potential who are sexually active with a non-sterilized male partner and sexually active men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) prior to study entry, for the duration of study participation, and for 3 months following completion of durvalumab. Method of contraception must be documented.

NOTE: Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

_____ 3.12 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up.

_____ 3.13 Patient must not have involvement in the planning and/or conduct of the study. No previous enrollment in the present study.

_____ 3.14 Patients may not have participated in another clinical study with an investigational product during the last 4 weeks.

_____ 3.15 Patients must not have any prior systemic therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, and other investigational agent) for mesothelioma.

_____ 3.16 No previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab or any other agent targeting immune checkpoints.

_____ 3.17 Patients must not have non-pleural mesothelioma e.g. mesothelioma arising in peritoneum, tunica vaginalis or any serosal surface other than the pleura.

_____ 3.18 Patients must not have an active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ.

NOTE: Patients with history of malignancy are not considered to have a "currently active" malignancy if they have completed therapy and are now considered by their physician to be at less than 30% risk for relapse.

_____ 3.19 Patients must not have mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction.

_____ 3.20 Patients must not have symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids (prednisone >10 mg or equivalent). Surgery, radiation and/or corticosteroids (any dose >10 mg prednisone equivalent) must have been completed ≥ 2 weeks prior to registration.

_____ 3.21 Patients must not have uncontrolled seizures.

_____ 3.22 Patients must not have current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Standard steroid premedication given prior to chemotherapy or as prophylaxis for imaging contrast allergy should not be counted for this criterion.

_____ 3.23 No active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel disease; Wegner syndrome) within the past 2 years. Subjects with vitiligo, alopecia, Grave's disease, or psoriasis not requiring systemic treatment (within the past 3 years) are not excluded.

_____ 3.24 No history of primary immunodeficiency.

_____ 3.25 No history of allogeneic organ transplant.

_____ 3.26 No history of hypersensitivity to durvalumab, cisplatin, carboplatin, pemetrexed or any of their excipients.

_____ 3.27 No uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

_____ 3.28 No active infection including tuberculosis (clinical evaluation including: physical examination findings, radiographic findings, positive PPD test, etc.), hepatitis B (known positive HBV surface antigen [HBsAg] result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies as defined by a positive ELISA test). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. HIV testing is not required in absence of clinical suspicion.

_____ 3.29 No known history of leptomeningeal carcinomatosis.

_____ 3.30 Patients must not have received live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.

_____ 3.31 Patients must not have any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

4. Registration Procedures

4.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with applicable US regulatory requirements and International Conference on Harmonization/Good Clinical Practice (ICH/GCP).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Freely given written informed consent must be obtained from every patient or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish patient eligibility for the trial.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of investigators or study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Investigators are responsible for the conduct of the study at their study site.

4.2 Regulatory Requirements

Before a site may enter patients, protocol-specific regulatory and other documents must be submitted to PrECOG as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Once required documents are received, reviewed, and approved by PrECOG or their representative, a Study Reference Manual (SRM) will be forwarded to the site. Any changes to site regulatory documents must be submitted by the investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. No patients will begin protocol therapy without formal registration as per the process below.

4.3 Patient Registration

Patients must not start protocol treatment prior to registration.

Patients must meet all of the eligibility requirements listed in Section 3 prior to registration. Treatment should begin ≤ 10 working days from study entry (date of registration).

An eligibility checklist is included in Section 3. A confirmation of eligibility assessment by the investigator and/or site will be performed during the registration process.

Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic data capture (eDC) system. Confirmation of registration will be displayed in the eDC system.

Full information regarding registration procedures and guidelines can be found in the SRM provided to your site. Correspondence regarding patient registration must be kept in the study records.

4.4 Research Tissue and Blood Samples

Mandatory tumor tissue samples are required to be available for enrollment.

Mandatory peripheral blood samples will also be collected.

Time points for tissue and blood samples are outlined in the study parameters (Section 10) and specific requirements are outlined in the correlative section of this protocol (Section 13) and the lab manual.

5. Study Design

5.1 Overview

This is a single arm, unblinded, open-label phase 2 study of durvalumab administered concurrently with pemetrexed/cisplatin chemotherapy as first-line treatment for unresectable pleural mesothelioma. The first six patients enrolled will be monitored for safety of the combination. A maximum of 55 patients (50 patients to be treated with expected ineligibility rate of 10%) will be enrolled and will receive up to 6 three week cycles of concurrent durvalumab with chemotherapy. Patients with responding or stable disease after six cycles of concurrent treatment will continue on durvalumab as a single agent administered once every 3 weeks. Maximum duration of durvalumab treatment is 12 months (inclusive of any treatment delays or missed treatments) starting from Cycle 1 of concurrent treatment.

Carboplatin may be substituted for cisplatin in patients with a documented contraindication (e.g., ototoxicity, renal function) to the use of cisplatin. These patients must otherwise fulfill the eligibility criteria (Section 3). In addition, for patients who receive cisplatin, carboplatin may also be substituted after Cycle 1 for cisplatin related toxicity (e.g., grade 3 ototoxicity, grade 3 nausea) at the investigator's discretion. Once carboplatin is substituted for cisplatin, patients cannot change back to cisplatin.

The study will be conducted at up to 26 US-based study centers.

All subjects will be evaluated regularly and their clinical status classified according to RECIST guidelines Version 1.1 [42] with modifications for pleural mesothelioma. All subjects will be followed for survival until the end of study (Section 7.2). AEs and SAEs will be followed as per Section 8. The objectives are described in Section 2.

5.2 Initial Enrollment of Six Patients with Safety Monitoring

As durvalumab has not been previously combined with pemetrexed platinum chemotherapy the study will commence with an initial enrollment of 6 patients who will receive pemetrexed and cisplatin (or carboplatin described in Section 3 and Section 5.1) combined with durvalumab for up to 6 cycles. After 6 cycles patients who have a PR or SD will continue on durvalumab until disease progression. In this initial run-in period subjects will be monitored for safety. The combination will be declared intolerable if ≥ 2 of the 6 patients experience a DLT defined in Section 6.2 occurring during the first 2 cycles of concurrent therapy phase.

The initial 6 patients completed 2 cycles of concurrent therapy with no DLTs.

The detailed statistical analysis plan is described in Section 12 of this protocol.

5.3 Expansion

The initial six patients were monitored for safety, without suspension to accrual and, the study will proceed with enrollment for a total of 55 patients

An Interim Safety Analysis on the first 15 patients who completed two cycles of therapy was also completed without suspension to accrual (Section 12.2.5 for details) and no safety concerns noted. It is expected that 50 of the 55 patients enrolled will receive treatment (ineligibility rate of 10%). Carboplatin may be substituted for cisplatin for patients with a documented contraindication (e.g., ototoxicity, renal function) to use of cisplatin and these patients must otherwise fulfill the eligibility criteria as noted in Section 3 and above in Section 5.1.

5.4 Evaluation of Subjects

Progression will be assessed using RECIST Version 1.1 modified for mesothelioma. Subjects will continue to receive treatment until disease progression or other discontinuation criteria are met. Removal of subject for clinical progression will be at the discretion of the Investigator. If a patient is deriving clinical benefit they may continue durvalumab (either

concurrent or single agent) until a repeat scan at least 4 weeks later (Section 9.1.5). Response assessments will be performed every 6 weeks for the first 18 weeks. After 18 weeks of treatment, response assessments will be performed every 9 weeks. The same method of assessment should be used throughout the study.

Following documentation of non-fatal confirmed disease progression, all subjects will be followed for survival (either routine clinic visit or telephone contact) every 3 months until death or the close of the study.

6. Treatment Plan

6.1 Overview

This is a single arm, open-label phase 2 study of durvalumab administered concurrently with pemetrexed/cisplatin (carboplatin may be substituted for cisplatin only as outlined in Section 3 and Section 5.1) chemotherapy as first-line treatment for unresectable pleural mesothelioma. The first six patients enrolled will be monitored for safety of the combination. A maximum of 55 patients will be enrolled and will receive up to six 3 week cycles of concurrent durvalumab with chemotherapy. Patients with responding or stable disease after 6 cycles of concurrent treatment will continue on durvalumab as a single agent administered once every 3 weeks. Maximum duration of durvalumab treatment is 12 months (inclusive of any treatment delays or missed treatments) starting from Cycle 1 of concurrent treatment.

6.1.1 Durvalumab Administration

Durvalumab will be administered before pemetrexed and cisplatin chemotherapy. Durvalumab 1120 mg will be administered by an infusion pump as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes will be considered a deviation.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Please refer to Section 11.1 and guidelines in Section 11.1.7 and Table 11-1.

6.1.2 Pemetrexed/Cisplatin Administration

The recommended dose of pemetrexed is 500 mg/m^2 administered as an intravenous infusion over 10 minutes (or per investigator discretion and local standard-of-care) on Day 1 of each 21-day cycle.

During concurrent treatment days, pemetrexed infusion will begin approximately 30 minutes after the infusion of durvalumab has finished (or per investigator discretion and local standard-of-care).

The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of pemetrexed administration (or per investigator discretion and local standard-of-care). Patients should receive appropriate hydration prior to and/or after receiving cisplatin. Hydration may commence prior to or concurrently with durvalumab.

If carboplatin is substituted for cisplatin per Section 3.9 and Section 5.1, the recommended dose of carboplatin is AUC 5 infused over 30 minutes beginning approximately 15-30 minutes after the end of the pemetrexed administration (or per investigator discretion and local standard-of-care).

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg) = (target AUC) x (CrCL by Cockcroft-Gault [Appendix II] + 25)

Please refer to Section 11.2 for additional information.

6.1.2.1 Pemetrexed Premedication

Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 µg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed has been administered. Intramuscular (IM)

injection of Vitamin B12 1000 µg should be given approximately one week prior to the first dose of pemetrexed and repeated on the day that the third and sixth pemetrexed treatment is administered. Oral folic acid and Vitamin B12 injection may also be given per local standard of care.

6.1.2.2 Cisplatin Premedication

Cisplatin will be administered to patients at least 30 minutes following the end of the pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care or use of 1 to 2 liters of fluid (per local standards) infused IV for 2-4 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standard-of-care.

6.1.2.3 Carboplatin Premedication

If carboplatin has been substituted for cisplatin per Section 3.9 or Section 5.1, premedication should follow local standard-of-care.

6.1.2.4 Antiemetics for use with Pemetrexed/Cisplatin (Carboplatin)

Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standard-of-care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

6.1.3 Pemetrexed/Cisplatin (or Carboplatin) Re-Treatment

Prior to each treatment with pemetrexed/cisplatin (carboplatin), the following conditions must be met.

- ANC must be ≥ 1500/mm^3 and platelets ≥ 100,000/mm^3 prior to the start of each cycle. Growth factor support is permitted, and should be administered per American Society of Clinical Oncology (ASCO) guideline.
- Pemetrexed: CrCL ≥ 45.
- Cisplatin: Serum creatinine ≤ 1.5 or CrCL ≥ 50.
    - Carboplatin may be substituted for cisplatin in patients with ≤ Grade 2 renal function at the investigator's discretion. Once carboplatin is substituted for cisplatin, patients cannot change back to cisplatin.
- Carboplatin: CrCL ≥ 45.
- All other drug-related non-hematologic toxicities must have improved to baseline or ≤ Grade 2. Exceptions to this criterion include alopecia and other toxicities of non-vital organs.

Treatment may be delayed for up to 3 weeks to allow sufficient time for recovery from treatment-related toxicities. If a delay greater than 3 weeks is required, the Investigator should confer with PrECOG to determine the appropriateness of continued treatment. In the event of a treatment delay, subsequent cycles should occur relative to the delayed cycle (maintaining a 3-week cycle interval). In other words, subsequent cycles should not be shortened to "make-up" for any delays.

6.2 Dose Limiting Toxicity - Definition

DLT, as defined below, will be evaluated for the first 2 cycles (2 doses) of concurrent therapy with durvalumab, pemetrexed and cisplatin. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 immune-mediated adverse event (imAE)
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 imAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation >8x ULN or total bilirubin >5x ULN

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility.
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities not associated with clinical signs or symptoms and reversed with appropriate maximal medical intervention within 3 days

Immune-mediated AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

6.2.1 DLT Assessment – Initial Enrollment of Six Patients

For the purposes of safety decision making during the initial enrollment of six patients, DLTs will be evaluated for the first 2 cycles (2 doses) of concurrent therapy with durvalumab, pemetrexed and cisplatin. DLTs occurring beyond this window will be taken into account when determining whether to proceed to enroll the full planned cohort of 55. DLTs will be monitored for the first 2 cycles (42 days) of concurrent therapy. Depending on the rate of accrual and review of the data pertaining to DLT evaluation, accrual may be halted to ensure it is safe to continue patient enrollment.

6.2.2 Phase II Treatment Administration

During the total enrollment of 55 patients (50 expected to commence therapy), toxicity will continue to be closely monitored. Because this is the first time that durvalumab is being combined with pemetrexed/cisplatin in this setting, close monitoring of toxicity is an important endpoint of the trial. We will also collect data and conduct an interim safety analysis among the first 15 patients who have completed the first 2 cycles (6 weeks) of concurrent therapy without suspension to accrual. The safety analysis will be done based on the electronic case report form (eCRF) database. This preliminary toxicity analysis will occur in addition to the twice yearly monitoring for toxicity for the purposes of interim reporting.

Interim analysis on first 15 patients who completed the first 2 cycles of concurrent therapy showed no safety concerns.

6.3 Dose Delays & Modifications

All toxicities should be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE V4.03). A copy of the CTCAE V4.03 can be downloaded from the CTEP website (http://www.ctep.cancer.gov).

A 3 day window is allowed for scheduled therapy, tests and/or results except as noted below for CBC with differential and platelet count. Delays due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

6.3.1 Durvalumab

For AEs that are considered at least partly due to administration of durvalumab, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (Table 6-1 and 6-2).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (Table 6-1 and 6-2). Dose reductions are not permitted for durvalumab.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune mediated Adverse Events (imAEs) during the conduct of this study. Potential imAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

NOTE: Patients with previous history of bleeding and/or are taking anticoagulant medication may have a higher risk of subsequent bleeding. Monitor patients closely for possible bleeding.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Tables 6-1 and 6-2, respectively.

Patients must have at least 2 cycles of pemetrexed/cisplatin (or carboplatin) with durvalumab in order to be eligible to proceed to maintenance durvalumab.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 8.2. All toxicities will be graded according to NCI CTCAE V4.03.

Table 6-1	**Dose Modifications and Toxicity Management Guidelines for Immune-Mediated Reactions Associated with Durvalumab**	
	Dose Modifications	**Toxicity Management**
Immune-Mediated Adverse Events (Overall Management For toxicities not noted below)	Drug administration modifications of study drug/study regimen will be made to manage potential immune-mediated AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE V4.03. In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/regimen. • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	It is recommended that management of immune-mediated adverse events (imAEs) follow the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indication of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. **General Recommendations:** – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone 1-2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).
	Grade 1 No dose modification Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1. • If toxicity worsens then treat as Grade 3 or Grade 4. – Study drug/study treatment can be resumed once event stabilizes to Grade ≤ 1 after completion of steroid taper. – Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) Event stabilizes and is controlled 2) Patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) Doses of prednisone are ≤ 10 mg/day or equivalent. Grade 3 Depending on the individual toxicity, may permanently discontinue study drug/ study regimen. Please refer to guidelines below.	

	Grade 4 Permanently discontinue study drug/ study regimen. **NOTE:** For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen. **NOTE:** Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper. **NOTE:** There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hypo or hyper-thyroidism, Type 1 diabetes mellitus)	– More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) - (also refer to individual sections of the imAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	Any Grade	**General Guidance**	– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (Radiographic Changes Only)** – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1. • If toxicity worsens then treat as Grade 3 or Grade 4. • If toxicity improves to ≤ Grade 1, then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (Mild to Moderate New Symptoms)** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1-2 mg/kg/day PO or IV equivalent). – Reimaging as clinically indicated. – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite IV methylprednisolone at 2-4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution:** Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[43] – Consider pulmonary and infectious disease consult. – Consider as necessary discussing with study physician.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening)** - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. - Obtain Pulmonary and Infectious disease consult, consider, as necessary, discussing with study physician. - Hospitalize the patient. - Supportive Care (oxygen, etc.). - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks dose) started. **Caution:** rule out sepsis and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[43]
Diarrhea/Colitis	Any Grade	**General Guidance**	- 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). - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections) including testing for clostridium difficile toxin, etc. - 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 event. - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observation only)	No dose modification	**For Grade 1 Diarrhea** - Close monitoring for worsening symptoms. - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	Grade 2 (Diarrhea: stool frequency of 4-6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to ≤ Grade 1. • If toxicity worsens then treat as Grade 3 or Grade 4. • If toxicity improves to ≤ Grade 1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2 Diarrhea** – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks.[44] **Caution:** Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to ≤ Grade 1 in 3-4 days. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥ 7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated)	Grade 3 Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤ 1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. Grade 4 Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 Diarrhea** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution:** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
Hepatitis (Elevated Liver Function Tests [LFTs]) **Infliximab should not be used for management of Immune Related Hepatitis**	Any Grade	**General Guidance**	– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT > to 3x ULN and/or Total Bili > to 1.5x ULN)	• No dose modification • If it worsens, treat as Grade 2 event	**For Grade 1 AST or ALT and/or Total Bili Elevation** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3 to ≤ 5x ULN and/or Total Bili >1.5 to ≤ 3.0 ULN)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1. • If toxicity worsens then treat as Grade 3 or Grade 4. • If toxicity improves to ≤ Grade 1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2 AST or ALT and or Total Bili Elevation** – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone PO or IV equivalent, consider additional work-up and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[45] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	Grade 3 (AST or ALT >5-20x ULN and/or Total Bili >3.0-10x ULN)	For elevations in transaminases ≤ 8x ULN, or elevations in bilirubin ≤ 5x ULN. • Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline. • Resume study drug/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days. For elevations in transaminases >8x ULN or elevations in bilirubin >5x ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3x ULN + bilirubin >2x ULN without initial findings of cholestasis (i.e. elevated Alkaline Phosphatase) and in the absence of any alternative cause.[46]	**For Grade 3 or 4 AST or ALT and/or Total Bili Elevation** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal workup, and imaging as appropriate. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
	Grade 4 (AST or ALT >20x ULN and/or Total Bili >10x ULN)	Permanently discontinue study drug/study regimen.	

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Any Grade	**General Guidance**	– Consult with Nephrologist. – 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, decrease in urine output, proteinuria, etc.). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.). – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 [Serum Creatinine >1-1.5x baseline; >ULN to 1.5x ULN]	No dose modification	**For Grade 1 Elevated Creatinine** – Monitor serum creatinine weekly and any accompanying symptom. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4. – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [Serum Creatinine >1.5-3.0x baseline; >1.5-3.0x ULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. • If toxicity worsens then treat as Grade 3 or Grade 4. • If toxicity improves to ≤ Grade 1 or baseline resume study drug/study regimen after completion of steroid taper.	**For Grade 2 Elevated Creatinine** – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted. – Consult Nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
			– Once improving gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine >3.0x baseline; >3.0-6.0x ULN Grade 4: Serum Creatinine >6.0x ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 Elevated Creatinine** – Carefully monitor serum creatinine on daily basis. – 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 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation].
Rash (excluding bullous skin formations)	Any Grade	**General Guidance**	Monitor for signs and symptoms of dermatitis (rash and pruritus) ****IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	**For Grade 1** – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1-2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3	**For Grade 2** – Obtain dermatology consult. – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
		• If toxicity improves to ≤ Grade 1 or baseline, then resume study drug/study regimen after completion of steroid taper.	– If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if persistent for >1-2 weeks or recurs.
	Grade 3	Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤ 1 or baseline within 30 days, then permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines (Appendix III)]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – Consider, as necessary, discussing with study physician.
	Grade 4	Permanently discontinue study drug/study regimen.	
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency, exocrine event of amylase/lipase increased)	Any Grade	**General Guidance**	– Consider consulting an Endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.). – Depending on suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine and related labs (e.g., blood glucose, ketone levels, HgA1c). – 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.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
			– If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modification	**For Grade 1: (including those with asymptomatic TSH elevation)** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning 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 < 0.5x LLN, or TSH >2x ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type I diabetes mellitus, hold study drug/study regimen dose until subject is clinically stable. • If toxicity worsens then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1) Event stabilizes and is controlled. 2) Patient is clinically stable as per Investigator or treating physician's clinical judgement.	**For Grade 2: (including those with symptomatic endocrinopathy)** – Consult endocrinologist to guide evaluation of endocrine function; and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, consider short-term, corticosteroids (e.g., 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy without study drug/study regimen interruption and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
		3) Doses of prednisone are ≤ 10 mg/day or equivalent.	– Once improving on steroids, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. • Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions. 1) The event stabilizes and is controlled. 2) The patient is clinically stable as per investigator or treating physician's clinical judgement. 3) Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For patients with abnormal endocrine work-up, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once improving on steroids, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
Immune Mediated Neurotoxicity (to include but not limited to limbic encephalitis, autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Any Grade	**General Guidance**	– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations). – Symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications	**For Grade 1** See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1. • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. ○ If toxicity worsens then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed once event improves to Grade ≤ 1 and after completion of steroid taper.	**For Grade 2** – Consider, as necessary, discussing with the study physician. – Obtain Neurology Consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.). – Promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent. – If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG).
	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 days.	**For Grade 3 or 4** – Consider, as necessary, discussing with study physician. – Obtain Neurology Consult. – Consider hospitalization.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	Grade 4	• Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG). – Once stable, gradually taper steroids over ≥ 28 days.
Immune-Mediated Peripheral Neuromotor Syndromes, such as Guillain-Barre and Myasthenia Gravis	Any Grade	**General Guidance**	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). 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, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 1	No dose modification	**For Grade 1** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	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 or autonomic instability.	**Grade 2** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology Consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.). *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	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 days or if there are signs of respiratory insufficiency or autonomic instability.	**For severe or life threatening (Grade 3 or 4) events** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	Grade 4	Permanently discontinue study drug/study regimen.	*MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
Myocarditis	Any grade	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis	– The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – 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). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, 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).

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2,3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	• If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue study drug/study regimen. • If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution:** It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
Myositis/Polymyositis ("Poly/myositis")	Any Grade	**General Guidance**	– 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, but rarely affects the extremities including hands and fingers; 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.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
			– 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 study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein 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. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	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 study physician.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	• 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. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – 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 3 to 5 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 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution:** It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	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 days or if there are signs of respiratory insufficiency. For Grade 4: Permanently discontinue study drug/study regimen	**For Grade 3 or 4 (severe or life-threatening events)** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – 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 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution:** It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.

	Grade of the Event (NCI CTCAE V4.03)	Dose Modifications	Toxicity Management
			– Consider whether patient may require IVIG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

Table 6-2 Dosing Modifications and Toxicity Management Guidelines for Non-Immune Mediated Reactions Associated With Durvalumab

CTC Grade/Severity (NCI CTCAE V4.03)	Dose Modification	Toxicity Management
Any Grade	**NOTE:** Dose modifications are not required for adverse events 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.
1	No dose adjustment	Treat accordingly as per institutional standard.
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline.	Treat accordingly as per institutional standard.
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly as per institutional standard.
4	Discontinue study drug/study regimen (**NOTE:** For Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with PrECOG).	Treat accordingly as per institutional standard.

6.3.2 Pemetrexed and Cisplatin (or Carboplatin)

Chemotherapy dose modifications will be performed according to Table 6-3 below. Subjects will be monitored for adverse events while receiving doublet chemotherapy regimens. Dose interruptions or reductions may be required. Chemotherapy dose modifications must be determined according to standard practice and clinical determination as to whether dose modification is necessary. Chemotherapy dose modifications are permanent; once the dose of any chemotherapy agent had been reduced it will remain reduced or be further reduced in subsequent cycles. The dose reductions are not linked and may be adjusted independently as summarized below.

Table 6-3 Dose Modifications for Pemetrexed, Cisplatin and Carboplatin

Dose Level	Pemetrexed	Cisplatin	Carboplatin
Starting Dose	500 mg/m^2	75 mg/m^2	AUC 5
First Dose Reduction	375 mg/m^2	56 mg/m^2	AUC 4
Second Dose Reduction	250 mg/m^2	38 mg/m^2	AUC 3
Third Dose Reduction	Stop Drug	Stop Drug	Stop Drug

NOTE: For renal toxicity, pemetrexed should be held when the CrCl <45 mL/minute. Caution should be used among subjects who are receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and who have mild to moderate renal insufficiency (CrCl between 45 and 79 mL/minute). Caution should also be used when nephrotoxic drugs are administered with pemetrexed.

Any subject with two prior dose reductions to one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent. A subject who is discontinued from the chemotherapy treatment will remain on the study and receive durvalumab as maintenance monotherapy as per the maintenance study calendar.

Patients must have at least 2 cycles of pemetrexed/cisplatin (or carboplatin) with durvalumab in order to be eligible to proceed to maintenance durvalumab provided:

1. Pemetrexed/cisplatin (or carboplatin) is discontinued before 6 cycles for toxicity reasons and the toxicity must have been attributable to the chemotherapy and not to the durvalumab.

   AND

2. Patients have either stable or responsive disease on imaging **OR** are continuing beyond progression per Section 9.1.5 (e.g., renal failure attributed to cisplatin and pemetrexed but not to durvalumab and scans show a response or are stable, patient could proceed to durvalumab maintenance).

6.4 Concurrent Therapies

6.4.1 Permitted

Investigators may prescribe 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 6.4.2.

6.4.2 Not Permitted

The following medications are not permitted during the study.

1. Any other investigational anticancer therapy.
2. Any other concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

   NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy). Palliative radiation may be given as clinically indicated and must start at least one week after dose of pemetrexed/cisplatin and/or durvalumab or must be completed at least one week before next dose of pemetrexed/cisplatin and/or durvalumab
3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
4. Live attenuated vaccines within 30 days of durvalumab dosing (i.e., 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine and the pneumococcal sub-unit or conjugate vaccine, are permitted. Herpes Zoster vaccine is a live attenuated vaccine and is not permitted.

6.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

The transfusion of blood products according to institutional practice is at the discretion of the investigator. Hematopoietic growth factors are permitted per ASCO guidelines as indicated for supportive care of patients. However, their use shall not be utilized to satisfy eligibility criteria for study entry.

7. Study Duration and Discontinuation of Therapy

7.1 Study Duration

Patients will receive protocol therapy unless:

1. Disease progression per modified RECIST Version.1.1 guidelines (notwithstanding the specific criteria for treatment beyond progression outlined in Section 9.1.5) or clinical progression.
2. Toxicities considered unacceptable by either the patient or the investigator, despite optimal supportive care and dose modifications.
3. Development of an inter-current illness that prevents further administration of study treatment.
4. Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.
5. Patient withdraws consent or is unable to comply with study procedures.

7.2 Duration of Follow-Up

Patients will be followed for adverse events for 90 days after their last dose of durvalumab or until initiation of alternative anticancer therapy.

If a patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment.

Following documentation of non-fatal confirmed disease progression, all subjects will be followed for survival (either routine clinic visit or telephone contact) every 3 months until death or the close of the study.

For patients who are registered but do not receive any protocol therapy, baseline and follow-up information per Section 10 will be collected.

7.3 Criteria for Removal from Study Treatment

A genuine effort will be made to determine the reason(s) why a patient fails to return for the necessary visits or is discontinued from the trial, should this occur. It will be documented whether or not each patient completed the clinical study. If for any patient study treatment or observations were discontinued, the reason will be recorded on the appropriate eCRF. Reasons that a patient may discontinue treatment in a clinical study are considered to constitute one of the following:

1. Recurrence of disease or documented progression of disease (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator).
2. Intercurrent illness that prevents further administration of treatment per investigator discretion.
3. Dose-limiting toxicity (Section 6.2 for definition of DLT).
4. Any AE that meets criteria for discontinuation as defined in Section 6.3.1, Table 6-1 and Table 6-2.
5. Unacceptable adverse events.
6. Grade ≥ 3 infusion reaction to durvalumab
7. Treatment interruption of more than 6 weeks after a scheduled treatment day.
8. Investigator discontinues treatment.
9. Initiation of alternative anticancer therapy including another investigational agent.
10. Pregnancy or intent to become pregnant.

11. Develop a second malignancy (except for non-melanoma skin cancer or cervical carcinoma in-situ) that requires treatment, which would interfere with this study.
12. The patient may choose to withdraw from the study at any time for any reason.
13. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.
14. Severe non-compliance to protocol as judged by the investigator.
15. Lost to follow-up.
16. Death.
17. Closure of study by PrECOG.

Any patient who receives at least one dose of study drug, durvalumab, will be included in the safety analysis. Patients who discontinue study treatment early should be followed for response assessments, if possible. Follow-up will continue per Section 10, as applicable.

8. Adverse Event Reporting

8.1 Collection of Safety Information

Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed).

After informed consent, but prior to initiation of study treatment (pemetrexed, cisplatin [or carboplatin], and/or durvalumab), only AEs/SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies). After the initiation of study treatment, all identified AEs and SAEs must be recorded and described on the appropriate page of the electronic Case Report Form (eCRF). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than individual symptoms. The following information should be documented for all AEs: date of onset and resolution, severity of the event; the investigator's opinion of the relationship to investigational product (see definitions below); treatment required for the AE treatment required for the AE; cause of the event (if known); and information regarding resolution/outcome.

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more-frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5x the ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF unless their severity, seriousness, or etiology changes.

Severity

The categories and definitions of severity used for clinical trials AEs are defined in the NCI's Common Terminology Criteria (CTCAE) V4.03 (http://ctep.cancer.gov/).

Attribution

The following categories and definitions of causal relationship or attribution to study drug should be used to assess Adverse Events:

- Definite: There is a reasonable causal relationship between the study drug and the event. The event response to withdrawal of study drug (dechallenge) and recurs with rechallenge, if clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the event. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is a reasonable causal relationship between the study drug and the event. Dechallenge information is lacking or unclear.

- Unlikely: There is doubtful causal relationship between the study drug and the event.
- Unrelated: There is clearly not a causal relationship between the study drug and the event or there is a causal relationship between another drug, concurrent disease, or circumstances and the event.

Categories 'definite', 'probable' and 'possible' are considered study drug related. Categories 'unlikely' and 'unrelated' are considered not study drug-related.

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

AEs related to pemetrexed and/or cisplatin (or carboplatin) should be followed for 30 days after last dose of study therapy or until the initiation of alternative anticancer therapy until ≤ grade 1 or stabilization, and reported as SAEs if they become serious.

Any AEs related to durvalumab should be followed for 90 days after last dose of durvalumab or until the initiation of alternative anticancer therapy until ≤ grade 1 or stabilization, and reported as SAEs if they become serious.

Any AE's (serious or not) that occur after the above time periods but are deemed to be at least possibly related to study therapy shall be reported.

8.2 Definition of Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to PrECOG. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an adverse event (AE) being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Colitis
- Pneumonitis/Interstitial Lung Disease (ILD)
- ALT/AST increases/hepatitis/hepatotoxicity
- Neuropathy/neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis/hypopituitarism, Type I diabetes mellitus, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis/Rash/Pruritis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)

- Myocarditis
- Hypersensitivity/Anaphylactic Reactions

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

8.2.1 Gastrointestinal Disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed.

Guidelines on management of diarrhea and colitis in patients receiving durvalumab are provided in Section 6.3.1, Table 6-1.

8.2.2 Pneumonitis

Adverse events of pneumonitis are of interest as pneumonitis has been reported with anti-PD-1 MAbs [47]. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Section 6.3.1, Table 6-1.

8.2.3 Hepatic Function Abnormalities (Hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies [48]. Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3x ULN and concurrent increase in total bilirubin to be greater than 2x ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Guidelines for management of subjects with hepatic function abnormality are outlined in Section 6.3.1, Table 6-1.

Cases where a subject shows an AST **or** ALT ≥ 3x ULN **or** total bilirubin ≥ 2x ULN may need to be reported as SAEs. 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.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.

- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3x ULN, one or more also show elevation of serum total bilirubin to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).

- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

8.2.4 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.

Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 6.3.1, Table 6-1.

8.2.5 Endocrine Disorders

Immune-mediated endocrinopathies include hypophysitis/hypopituitarism, Type I diabetes mellitus, adrenal insufficiency, and hyper- and hypothyroidism.

Guidelines for the management of patients with immune-mediated endocrine events are provided in Section 6.3.1, Table 6-1.

8.2.6 Nephritis

Consult with Nephrologist. 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, decrease in urine output, proteinuria, etc.).

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.

Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 6.3.1, Table 6-1.

8.2.7 Pancreatic Disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation.

Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Section 6.3.1, Table 6-1.

8.2.8 Myocarditis

Immune-mediated myocarditis includes decreased ejection fraction, arrhythmias, and in particular occurrences of atrioventricular block.

For patients with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection) and the appropriate management that includes discontinuing drug (permanently if biopsy-proven immune-mediated myocarditis) and the prompt use of steroids or other immunosuppressives. Patients with pre-existing cardiac disorders should be closely monitored for deterioration in their cardiac condition, which could suggest new onset myocarditis.

8.2.9 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy [48]. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion related reactions are outlined in Section 6.3.1, Table 6-1.

8.3 Handling of Serious Adverse Events (SAEs)

8.3.1 SAE Definitions

A ***serious AE*** is any untoward medical occurrence occurring after initiation of study treatment or that at any dose:

- results in death
- is life-threatening (defined as an event in which the study patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

8.4 SAE Reporting Requirements

Serious adverse events (SAE) are defined above. The investigator should inform PrECOG of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on the PrECOG SAE form. This form must be completed and supplied to PrECOG within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up PrECOG SAE report form. A final report to document resolution of the SAE is required. The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation. A copy of the fax transmission confirmation of the SAE report to PrECOG should be attached to the SAE and retained with the patient records.

All SAEs should be faxed to 888-276-9606 or scanned and emailed to PrE0505SAE@qdservices.com as per the instructions found in study materials provided to the investigator site.

[redacted]
Medical Monitor
During normal business hours
(8:30 am-5:00 pm EST):
Phone: 610-354-0404
After normal business hours:
Phone: 484-574-2367
Email: [redacted]

Manager, Clinical Safety
During normal business hours
(8:30 am-5:00 pm EST):
Phone: 610-354-0404
After normal business hours:
Cell: 484-574-2367

PrECOG will notify AstraZeneca of all SAE's within 24 hours of PrECOG's Awareness Date as discussed above. Relevant follow-up information will be provided to AstraZeneca as soon as it becomes available.

Investigators should also report event(s) to their IRB as required.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

All SAEs, regardless of causality (Section 8.4.1 for additional information for hepatic function abnormality) must be collected which occur within 90 days of last dose of durvalumab or until the initiation of alternative anticancer therapy. This includes all deaths within 90 days of last dose of durvalumab, unless related to progression of disease (disease progression will be documented, but not reported as an SAE). After 90 days, patients with ongoing durvalumab-related SAEs will be continued to be followed for safety.

In addition, if a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, durvalumab-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The Investigator should notify PrECOG or designee of any SAE that may occur after the above time period which they believe to be definitely, probably or possibly related to investigational product.

NOTE: After study closure, study-drug related SAEs should be reported voluntarily by the treating physician to the manufacturer.

Serious adverse event reporting to regulatory authorities and all participating investigators will be conducted by PrECOG (or designee) in accordance with 21CFR312.32, local requirements and international regulations, as appropriate. FDA reporting requirement timelines will be followed. PrECOG will also concurrently forward any such reports to AstraZeneca.

8.4.1 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 8.2.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** as noted above, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by PrECOG.

8.5 Reporting of Other Second Primary Cancers

New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

All cases of new primary cancers that occur during or after protocol treatment must be reported to PrECOG on a Second Primary Cancer form within 30 days of diagnosis, regardless of relationship to protocol treatment. Secondary primary malignancies should also be reported as a SAE. The SAE form is not for use for reporting recurrence or development of metastatic disease. A copy of the pathology report, if applicable, should be sent, if available.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted.

8.6 Procedures in Case of Pregnancy

Prior to study enrollment, women of childbearing potential (WOCBP) and male patients with a female partner of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy, documented in the informed consent.

8.6.1 Maternal Exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drugs may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform PrECOG within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

PrECOG will work with the Investigator to ensure that all relevant information is provided to PrECOG within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.6.2 Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

8.7 Durvalumab Overdose

An overdose is defined as a subject receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to PrECOG. If the overdose results in an AE, the AE must also be recorded as an AE (Section 8.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (Section 8.4). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose either of durvalumab or the chemotherapeutic agents used to treat patients enrolled in this protocol.

9. Measurement of Effect

9.1 Solid Tumor Response Criteria (RECIST Version 1.1)

9.1.1 Malignant Disease Evaluation

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline Version 1.1 with standard modifications used in the evaluation of mesothelioma [42, 49-50]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.

The term evaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

9.1.1.1 Measurable

Measurable tumor lesions are those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- ≥ 10 mm by CT scan (irrespective of scanner type) and MRI (*no less than double the slice thickness and a minimum of 10 mm*)
- ≥ 10 mm caliper measurement by clinical exam (when superficial)
- ≥ 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung)

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

9.1.1.2 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis (perpendicular to longest diameter) when assessed by CT scan.

9.1.1.3 Non-Measurable

All other lesions (or sites of disease), including small lesions not meeting the criteria in 9.1.1.1 and 9.1.1.2, are considered non-measurable lesions. This includes lymph nodes measured at ≥ 10 to <15 mm in the short axis. **NOTE:** Lymph nodes measured at <10 mm in the short axis are considered normal.

Lesions considered to be non-measurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by

physical exam that is not measurable by reproducible imaging techniques.

NOTE: 'Cystic lesions' that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability in Section 9.1.1.1. Blastic bone lesions are non-measurable.

Tumor lesions that are situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

9.1.2 Definitions of Response

9.1.2.1 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameters), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

The sum of the target lesions (longest diameter for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters/axes will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

<u>Complete Response (CR)</u>

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

<u>Partial Response (PR)</u>

At least a 30% decrease in the sum of the diameters/axes of target lesions, taking as reference the baseline sum diameters/axes. To be assigned a status of partial response, changes in tumor measurements

must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response is met.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters/axes of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm over the nadir. (**NOTE:** the appearance of one or more new lesions is also considered progression).

Please refer to Section 9.1.5 for Immune-Related Response for guidance.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters/axes while on study. (**NOTE:** a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease).

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

9.1.2.2 Non-Target Lesions

All other lesions or sites of disease including any measurable lesions over and above the 5 target lesions and lymph nodes measured at ≥ 10 to <15 mm in the short axis should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

Complete Response (CR)

The disappearance of all non-target lesions and normalization of tumor marker levels, if applicable. All lymph nodes must be non-pathological in size (<10 mm short axis). To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD

The persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker levels above the normal limits. To be assigned a status of Non-CR/Non-PD, measurements must have met the Non-CR/Non-PD criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

Progressive Disease (PD)

The appearance of one or more new lesion(s) and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be

representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

Please refer to Section 9.1.5 for Immune-Related Response for guidance.

9.1.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD) however this should lead to clinical evaluation as guided by Section 9.1.5 below.

9.1.4 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

9.1.5 Immune-Related Response

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following [51, 52]:

- Response to immunotherapy may be delayed.
- Response to immunotherapy may occur after PD by conventional criteria.
- The appearance of new lesions may not represent PD with immunotherapy.
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) [53] for immune modulating anti-cancer compounds, the study will implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab would continue between the initial assessment of progression and confirmation for progression.

- In addition, subjects may continue to receive durvalumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria modified for mesothelioma.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than durvalumab or with symptomatic progression that requires urgent medical intervention (e.g., symptomatic central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.2 Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from the start of the treatment until confirmed disease progression or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Assessment of best overall response should allow for immune-related response patterns as described in Section 9.1.5. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (Table 9-1).

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

Table 9-1: Overall Response for All Possible Combinations of Tumor Response

Target Lesions	Non-Target Lesions	New Lesion	Overall Response	Remarks
CR	CR	No	CR	Confirmation at ≥ 4 weeks
CR	Non-CR/Non-PD*	No	PR	Confirmation at ≥ 4 weeks
CR	Not Evaluated	No	PR	Confirmation at ≥ 4 weeks
PR	Non-PD*/Not Evaluated	No	PR	Confirmation at ≥ 4 weeks
SD	Non-PD*/Not Evaluated	No	SD	Documented at least once ≥ 4 weeks from study entry
Not All Evaluated	Non-PD	No	Not Evaluable	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD*	
Any	Any	Yes	PD	

* PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to Section 9.1.2.2 Non-Target Lesions-Progressive Disease for further explanation.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

NOTE: If subjects respond to treatment and are able to have their disease resected; the patient's response will be assessed prior to the surgery. However, the patient will be considered inevaluable for survival analysis.

9.2.1 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality should be used throughout the study to measure disease (preferred but not mandated).

9.2.1.1 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

9.2.1.2 CXR

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

9.2.1.3 CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

9.2.1.4 PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the

CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

9.2.1.5 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

9.2.1.6 Endoscopy, Laparoscopy

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

9.2.1.7 Tumor Markers

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

9.2.1.8 Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is mandatory to differentiate between response or SD (an effusion may be a side effect of the treatment) and PD.

10. Study Parameters

1. All pre-study scans should be done ≤ 4 weeks prior to registration.
2. All other pre-study assessments should be done ≤ 2 weeks prior to registration.

Concurrent Treatment Phase - Chemotherapy with Durvalumab												
Procedures	**Screening**	**Cycle 1* (1 Cycle = 21 Days)**				**Cycle 2 to Cycle 6***				**Every 6 weeks During Concurrent Phase of Protocol***	**Off Treatment[20]**	**Follow-Up[22]**
		Day 1	**Day 8[1]**	**Day 15**	**Day 21**	**Day 1**	**Day 8**	**Day 15**	**Day 21**			
Written Informed Consent[2]	X											
Disease Characteristics[3]	X											
Medical/Surgical History	X											
Assessment of Baseline Signs & Symptoms	X											
Height	X											
Physical Exam including[4] Weight	X	X	X			X					X	
Vital Signs (Temperature, Pulse, Blood Pressure)[5]	X	X	X			X					X	
Body Surface Area (BSA)	X	X				X						
Performance Status	X	X	X			X					X	
Electrocardiogram[6]	X	X[6]	As clinically indicated									
CBC/Differential/Platelets[7]	X	X	X			X					X	
Chemistry[8]	X	X	X			X					X	
TSH[9]	X	X				X						

Concurrent Treatment Phase - Chemotherapy with Durvalumab												
Procedures	**Screening**	**Cycle 1* (1 Cycle = 21 Days)**				**Cycle 2 to Cycle 6***				**Every 6 weeks During Concurrent Phase of Protocol***	**Off Treatment[20]**	**Follow-Up[22]**
		Day 1	**Day 8[1]**	**Day 15**	**Day 21**	**Day 1**	**Day 8**	**Day 15**	**Day 21**			
Hepatitis B & Hepatitis C[10]	X											
PT/INR	X	As Clinically Indicated										
Urinalysis[11]	X	X				X						
Urine or Serum Pregnancy Test[12]	X	As Clinically Indicated										
Brain MRI or CT with Contrast[13]	X											
Chest CT with Contrast and Abdomen MRI or CT with Contrast	X											
Chest CT with Contrast & MRI or CT of any other Disease Sites										X[19]	X[20]	
Archived Tumor Tissue Procurement (Mandatory)[14]	X											
Research Blood Specimens (Mandatory)[15]		X				X[15]						
Treatment Administration[16]		X				X						
Palliative Radiation Therapy[17]	As clinically indicated											
Concomitant Medication Review[18]	X	X	X			X					X	
Adverse Events Assessment		X	X			X					X[21]	
Survival Status												X

* **Scheduled Visits:** +/- 3 day window for therapy/tests/visits during therapy. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

1 Day 8 visit only required on Cycle 1 of concurrent phase of treatment for the 6 safety run-in patients.

2 Repeat Informed consent is required for patients continuing on treatment past initial RECIST progression (Section 9.1.5).

3 Record date of diagnosis, primary tumor type, histology, stage.

4 Full physical examination at baseline, targeted physical examination at other time points.

5 Patients will have Temperature, Pulse and Blood Pressure taken at each visit. In addition, patients will have their blood pressure and pulse measured before, during and after the durvalumab infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from start of the infusion) (±5 minutes) for the first infusion only and then for subsequent infusions as clinically indicated.

NOTE: If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

6 ECG during Screening (in triplicate). Cycle 1, Day 1- ECG (single tracing) should be taken within an hour prior to the start of the durvalumab infusion and at one time point 0 to 3 hours after the cisplatin (or carboplatin) infusion, thereafter as clinically indicated. Screening and abnormal ECG at any time in triplicate (2-5 minutes apart); others single tracing.

7 CBC with differential and platelet count which includes WBC, ANC, Platelets, Hemoglobin, and Hematocrit required prior to each dose of treatment (Day 1 of each cycle and on Day 8 of Cycle 1 only), and results known prior to treatment administration.

8 Albumin, BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, magnesium, alkaline phosphatase, AST, ALT, total bilirubin, LDH and total protein. Gamma-glutamyltransferase (GGT), amylase and lipase testing at Screening, and as clinically indicated.

9 Free T_3 and free T_4 will only be measured if TSH is abnormal. Free T_3 and free T_4 should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

10 Hepatitis B (HBV surface antigen [HBsAg]) and hepatitis C (HCV antibody) testing. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11 Patients with previous history of bleeding and/or are taking anticoagulant medication may have a higher risk of subsequent bleeding. Monitor patients closely for possible bleeding.

12 Pre-menopausal female subjects of childbearing potential only.

13 Subjects with neurologic or other symptoms concerning for possible central nervous system (CNS) involvement should have a Brain MRI or Brain CT with contrast during the screening period.

14 Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery. Formalin-Fixed Paraffin-Embedded (FFPE) block (preferred) or a minimum of 15 FFPE unstained sections of 5 micron thickness plus 1 H&E slide will be required. Procurement of tissue will be mandatory for enrollment. Submit tumor sample (block or slides) within 3 months of patient registration. See Section 13.1 and 13.3 for details.

15 Research bloods are to be drawn prior to treatment on C1D1, prior to treatment on C2D1, and prior to treatment on C5D1 of concurrent therapy or **at time of confirmed progression IF confirmed progression occurs before Cycle 5, Day 1.**

At each time point, collect one (1) 10 mL EDTA tube and two (2) 10 mL Streck tubes. **EDTA tube must be collected before the Streck tubes**. Details of blood specimen handling and shipping are provided in the lab manual. See Section 13.1 and 13.4 for details.

16 Patients will receive **durvalumab 1120 mg, pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (or carboplatin AUC 5)** by IV infusion on days 1 of each 21 day cycle (1 cycle=21 days). Up to 6 cycles (6 doses) of concurrent therapy will be administered. See Section 6.1 for administration and re-treatment guidelines and Section 6.3.1, Table 6-1 and Table 6-2 for dose modifications for durvalumab and Section 6.1 for administration and re-treatment guidelines and Section 6.3.2 and Table 6-3 for dose modifications/reductions for pemetrexed and cisplatin (or carboplatin). Patients must have at least 2 cycles of pemetrexed/cisplatin (or carboplatin) with durvalumab in order to be eligible to proceed to maintenance durvalumab (Section 6.3.2 for additional guidelines).

NOTE: Oral folic acid 350 to 1000 µg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed has been administered. Intramuscular (IM) injection of Vitamin B12 1000 µg should be given approximately one week prior to the first dose of pemetrexed and repeated on the day that the third and sixth pemetrexed treatment is administered. Oral folic acid and Vitamin B12 injection may also be given per local standard of care.

17 Palliative radiation may be given as clinically indicated and must start at least one week after dose of pemetrexed/cisplatin and durvalumab or must be completed one week before next dose of pemetrexed/cisplatin and durvalumab.

18 Review of prior/concomitant medication taken 14 days prior to informed consent and continues until completion of study treatment.

19 Beginning with Cycle 1 radiographic response will be assessed with imaging every 6 weeks until completion of concurrent phase of treatment. In the setting of progressive disease on a single tumor assessment, patients will be made aware of the potential benefits and risks of continuing the study regimen in the setting of PD by providing separate written informed consent (Section 9.1.5 for criteria for treatment beyond progression).

20 If more than 4 weeks since last scan, repeat MRI and/or CT to confirm disease status/progression. If patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment.

21 Patients will be followed for adverse events related to cisplatin (or carboplatin) and/or pemetrexed for 30 days after their last dose of study therapy or for 90 days after their last dose of durvalumab or until the initiation of alternative anticancer therapy.

22 Every 3 months from treatment discontinuation until death or study closure. Initiation of any other anti-cancer therapies will also be documented.

Monotherapy with Durvalumab							
Procedures	**Each Cycle* 1 Cycle = 21 Days**				**Every 9 Weeks During Maintenance Phase***	**Off Treatment[11]**	**Follow-Up[13]**
	Day 1	**Day 8**	**Day 15**	**Day 21**			
Written Informed Consent[1]							
Physical Exam including Weight[2]	X					X	
Vital Signs (Temperature, Pulse, Blood Pressure)[3]	X					X	
Body Surface Area (BSA)	X						
Performance Status	X					X	
Electrocardiogram[4]	As clinically indicated						
CBC/Differential/Platelets[5]	X					X	
Chemistry[6]	X					X	
TSH[7]	X						
Urinalysis	X						
Chest CT with Contrast & MRI or CT of any other Disease Sites					X[10]	X[11]	
Treatment Administration[8]	X						
Concomitant Medication Review	X					X	
Palliative Radiation Therapy[9]	As clinically indicated						
Adverse Events Assessment	X					X[12]	
Survival Status							X

* **Scheduled Visits:** +/- 3 day window for therapy/tests/visits during therapy. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

1 Repeat Informed consent is required for patients continuing on treatment past initial RECIST progression (Section 9.1.5).

2 Full physical examination for first cycle of Maintenance therapy; targeted physical examination at other time points.

3 Patients will have Temperature, Pulse and Blood Pressure taken at each visit. In addition, patients will have their blood pressure and pulse measured before, during and after the durvalumab infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)

NOTE: If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

4 ECG as clinically indicated. Abnormal ECG at any time in triplicate (2-5 minutes apart); others single tracing.

5 CBC with differential and platelet count which includes WBC, ANC, Platelets, Hemoglobin, and Hematocrit required prior to each dose of treatment (Day 1 of each cycle), and results known prior to treatment administration.

6 Albumin, BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, magnesium, alkaline phosphatase, AST, ALT, total bilirubin, LDH and total protein. GGT, amylase and lipase testing as clinically indicated.

7 Free T_3 and free T_4 will only be measured if TSH is abnormal. Free T_3 and free T_4 should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

8 Patients will receive **durvalumab 1120 mg** by IV infusion on days 1 of each 21 day cycle (1 cycle=21 days). Maximum duration of 12 months of durvalumab (starting from Cycle 1 of concurrent treatment) will be administered. See Section 6.1 for administration guidelines and Section 6.3.1, Table 6-1 and Table 6-2 for dose modifications for durvalumab.

9 Palliative radiation may be given as clinically indicated and must start at least one week after dose of durvalumab or must be completed one week before next dose of durvalumab.

10 During maintenance durvalumab tumor restaging will be once every 9 weeks. In the setting of progressive disease on a single tumor assessment, patients will be made aware of the potential benefits and risks of continuing the study regimen in the setting of PD by providing separate written informed consent (Section 9.1.5 for criteria for treatment beyond progression).

11 If more than 4 weeks since last scan, repeat MRI and/or CT to confirm disease status/progression. If patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment.

12 Patients will be followed for adverse events for 90 days after their last dose of durvalumab or until the initiation of alternative anticancer therapy.

13 Every 3 months from treatment discontinuation until death or study closure. Initiation of any other anti-cancer therapies will also be documented.

11. Drug Formulation and Procurement

11.1 Durvalumab

11.1.1 Other Names

Also known as MEDI4736.

11.1.2 Classification

Human IgG1κ monoclonal antibody.

11.1.3 Mode of Action

[redacted]

11.1.4 Storage

Unopened vials of MEDI4736 lyophilized or liquid Drug Product must be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

11.1.5 Dose Specifics

A fixed dose of 1120 mg q 3 weeks durvalumab will be used in this study.

For patients weighing ≥ 30 kg, a fixed dose of 1120 mg Q3W durvalumab (equivalent to 15 mg/kg Q3W based on an average body weight of 75 kg) should be prepared. Patients <30 kg body weight should be discussed with PrECOG before considering patient for enrollment.

Refer to Section 6.3.1 and Table 6-1 and Table 6-2 for Dose Delays and Modifications details.

11.1.6 Preparation

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. [redacted] The nominal fill volume is 10 mL Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

Preparation of Durvalumab Doses for Administration with an IV Bag

The dose of durvalumab for administration must be prepared using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1120 mg durvalumab for patient's ≥ 30 kg will be administered using an IV bag containing 0.9% (w/v) saline with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Remove a volume of IV solution from the IV bag equal to the calculated volume of durvalumab to be added to the IV bag prior to addition of durvalumab. Next, the volume of durvalumab (i.e., 15.0 mL for 750 mg or 30.0 mL for 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

11.1.7 Route of Administration

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline) equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

Table 11-1 Durvalumab Hold and Infusion Times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined above, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

11.1.8 Monitoring of Dose Administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in Section 10. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

11.1.9 Management of Infusion Reaction

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤ Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. Steroids should not be used for routine premedication of ≤ Grade 2 infusion related reactions.

If the infusion related reaction is Grade 3 or higher in severity, study drug will be discontinued.

The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

11.1.10 Availability

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution.

The initial supply of durvalumab will be sent directly to the site upon site activation. As needed, durvalumab may be requested by the PI (or their authorized designees) at each participating institution. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return/destruction (site's drug destruction policy must be reviewed and approved by PrECOG before any study drug can be destroyed at a site) of durvalumab.

11.1.11 Agent Ordering

PrECOG will be responsible for ordering drug for re-supply to the site. Requests for shipments of durvalumab will be coordinated between PrECOG and AstraZeneca.

11.1.12 Agent Accountability

Durvalumab will be stored in a secure location. Only authorized pharmacy and study staff will have access to this agent. Drug accountability will be performed by PrECOG.

11.2 Pemetrexed [36] and Cisplatin [37]

NOTE: Pemetrexed and Cisplatin (carboplatin may be substituted for cisplatin as described in Section 3.9 and Section 5.1) will be obtained by the individual study sites as standard of care treatments from commercial stock. Refer to commercial package inserts for full prescribing information.

11.2.1 Other Names

Pemetrexed - Alimta®

Cisplatin – Platinol®

Carboplatin [38] – Paraplatin®

11.2.2 Classification

Pemetrexed is a folate analog metabolic inhibitor indicated for the treatment of mesothelioma in combination with cisplatin.

Cisplatin and Carboplatin are alkylating agents that appear to form intra- and inter-strand crosslinks in cells which modifies DNA structure and inhibits DNA synthesis.

11.2.3 Storage and Stability

Please consult the prescribing information for Pemetrexed, Cisplatin and Carboplatin.

11.2.4 Dose Specifics

Recommended dose of pemetrexed is 500 mg/m^2 IV on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m^2 IV beginning 30 minutes after pemetrexed administration (or per investigator discretion and local standard-of-care).

If carboplatin is substituted for cisplatin per Section 3.9 or Section 5.1, the recommend dose of Carboplatin is AUC of 5 on Day 1 of each 21-day cycle beginning 15-30

minutes after pemetrexed administration (or per investigator discretion and local standard-of-care)..

11.2.5 Preparation

Pemetrexed and cisplatin (or carboplatin) will be prepared as per the institutional standards.

11.2.6 Route of Administration

The recommended dose of pemetrexed is 500 mg/m^2 administered as an intravenous infusion over 10 minutes (or per investigator discretion and local standard-of-care) on Day 1 of each 21-day cycle.

During concurrent treatment days, **pemetrexed infusion will begin approximately 30 minutes after the infusion of durvalumab has finished** (or per investigator discretion and local standard-of-care).

The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of pemetrexed administration (or per investigator discretion and local standard-of-care). Patients should receive appropriate hydration prior to and/or after receiving cisplatin. Hydration may commence prior to or concurrently with durvalumab. See cisplatin package insert for more information.

If carboplatin is substituted for cisplatin per Section 3.9 or Section 5.1, the recommended dose of carboplatin is AUC 5 infused over 30 minutes beginning approximately 15-30 minutes after the end of the pemetrexed administration (or per investigator discretion and local standard-of-care).

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg) = (target AUC) x (CrCL by Cockcroft-Gault [Appendix II] + 25)

NOTE: With the Calvert formula, the total dose of PARAPLATIN is calculated in mg, not mg/m^2.

11.2.7 Incompatibilities

Please consult the prescribing information for Pemetrexed, Cisplatin and Carboplatin.

11.2.8 Premedication Regimen – Pemetrexed

Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 µg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed has been administered. Intramuscular (IM) injection of Vitamin B12 1000 µg should be given approximately one week prior to the first dose of pemetrexed and repeated on the day that the third and sixth pemetrexed treatment is administered. Oral folic acid and Vitamin B12 injection may also be given per local standard of care.

11.2.9 Premedication Regimen – Cisplatin

Cisplatin will be administered to patients at least 30 minutes following the end of the pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care or use of 1 to 2 liters of fluid (per local standards) infused IV for 2-4 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standard-of-care.

11.2.10 Premedication Regimen - Carboplatin

If carboplatin has been substituted for cisplatin per Section 3.9 or Section 5.1, premedication should follow local standard-of-care.

11.2.11 Antiemetics for use with Pemetrexed/Cisplatin (Carboplatin)

Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standard-of-care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

12. Statistical Considerations

12.1 Study Design & Sample Size Considerations – Safety Run-In

12.1.1 Study Design and Objectives – Initial Six Patients Enrolled

It is planned to enroll a total of 55 patients (50 expected to receive treatment) on this study, the first six patients enrolled will be monitored for safety of the combination of durvalumab with pemetrexed/cisplatin (or carboplatin). Standard induction with pemetrexed/cisplatin (or carboplatin) will be given for six 3-week cycles with the addition of concurrent durvalumab dosed at 1120 mg every 3 weeks. After completion of Cycle 6 of concurrent therapy, patients with stable or responding disease per modified RECIST for malignant mesothelioma will continue on single agent durvalumab at the same dose every 3 weeks until disease progression or a maximum duration of 12 months of durvalumab starting from Cycle 1 of concurrent treatment.

The initial 6 patients completed 2 cycles of concurrent therapy with no DLTs.

12.1.2 Statistical Analysis Plan for Safety

This study will initially enroll 6 patients (from the total of 50 patients expected to enroll and receive treatment) to the combination of pemetrexed/cisplatin (or carboplatin) with durvalumab. The combination will be declared intolerable if ≥ 2 of the 6 patients experience a DLT (defined as in Section 6.2) during the first 2 cycles of concurrent therapy. The table below summarizes the probability of declaring this combination safe for range of true but unknown DLT rates:

True DLT rate	10%	20%	30%	40%	50%
Probability of <2 DLTs among 6 patients	0.89	0.66	0.42	0.23	0.11

Upon completion of the trial, we will summarize the total number of patients enrolled on the study, and provide summaries of toxicity rates. We will also review and tabulate the DLTs.

12.1.3 Sample Size Considerations

The study will proceed to enroll a total of 55 patients if **<**2 patients among the first 6 patients enrolled experience a DLT. Depending on the rate of accrual and review of the data pertaining to DLT evaluation, accrual may be halted to ensure it is safe to continue patient enrollment.

12.1.4 Monitoring Plan

While the initial six patients are receiving treatment, the study team will meet via teleconference to review and discuss DLTs and the overall trial conduct.

12.2 Expansion Phase

12.2.1 Expansion Study Design and Objectives

The initial six patients were monitored for safety, without suspension to accrual and, the study will proceed with enrollment of a total of 55 patients of whom it is expected 50 patients will receive treatment (ineligibility rate of 10%). This is a single arm phase II study evaluating the benefit of durvalumab in combination with pemetrexed/cisplatin (or carboplatin) for the treatment of first-line unresectable pleural mesothelioma. Durvalumab will be administered concurrently with Cycle 1-6 of first line pemetrexed and cisplatin (or carboplatin) followed by maintenance durvalumab until disease progression or a maximum duration of 12 months of durvalumab starting from Cycle 1 of concurrent treatment. The primary objective of this phase II study is overall survival.

Secondary objectives include progression-free survival, objective response, immune-related response, toxicity, and correlatives which will include association of PD-L1 expression with clinical outcomes.

12.2.2 Phase II Endpoints

Overall survival (OS) is defined as the time from randomization to death from any cause. Patients that have not had an event reported at analysis will be censored at their date of last follow-up.

Progression-free survival (PFS) is defined as the time from randomization to documented disease progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free.

Best objective response will be evaluated via RECIST Version 1.1 criteria modified for mesothelioma, as described in the Section 9.

Immune-related response will be evaluated using the Wolchok criteria [51].

Toxicity will be determined using the CTCAE Version 4.03 criteria.

12.2.3 Phase II Statistical Analysis Plan

The primary and some secondary analyses will include all eligible patients who started assigned therapy including the first six patients evaluated for safety.

OS and PFS distributions will be estimated using the Kaplan-Meier method, and Cox proportional hazards models will be used to estimate the hazard ratios among subgroups. The primary test for OS will be based on the Wald test for the log failure rate parameter and tested at a one-sided type I error rate of 10%. Any comparisons of subgroups will be made using the logrank test and Cox modeling.

If toxicity rates are compared between subgroups, Fisher's exact tests with a one-sided type I error rate of 10% will be used; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes.

Point estimates of all endpoints will be accompanied by the corresponding 95% confidence intervals.

In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned because we do not anticipate an excess of missing data.

Subset analyses are planned for known prognostic factors such as performance status, age, gender, etc. Subset analyses of all variables, including correlatives, are considered to be exploratory in nature.

12.2.4 Phase II Sample Size Considerations

The primary comparison will include all eligible patients who started protocol treatment, of whom 50 will be accrued. After inflating for an ineligibility rate of 10%, the total planned accrual is 55 patients. Based on the randomized phase III trial conducted by Vogelzang in this setting [39], we assume that the null hypothesis is that the median OS is 12 months with pemetrexed/cisplatin alone (refer to Section 1. for additional historical background information). Using a one-sided 0.10 level test, we will have 90% power to detect a 37% reduction in the OS hazard rate of 0.058 to 0.037 (with an accrual period of 24 months for the 50 patients in the primary analysis, and an additional 18 months for treatment and follow-up); assuming exponential survival, this corresponds to a 58% improvement in the median OS of 12 months to 19 months.

The number of OS events needed to achieve this power is 32 events.

12.2.5 Interim Toxicity Assessment

Because this is the first time that durvalumab is being combined with pemetrexed/ cisplatin (or carboplatin) in this setting, close monitoring of toxicity is an important endpoint of the trial. We will collect data and conduct an interim safety analysis among the first 15 patients who have completed the first two cycles of tri-modal therapy without suspension to accrual. The safety analysis will be done based on the eCRF. This preliminary toxicity analysis will occur in addition to the twice yearly monitoring for toxicity for the purposes of interim reporting. The probability that 5 or more Grade 4/5 events are observed among the first 15 patients is 0.03 if the true Grade 4/5 non-hematologic toxicity rate is 12% as expected based on trials of pemetrexed/cisplatin in lung cancer and mesothelioma. This probability increases to 0.88 if the true rate of Grade 4/5 non-hematologic toxicity is 0.45. Therefore, we will suspend accrual for further review of non-hematologic toxicity if we observe at least 5 Grade 4/5 non-hematologic events among the first 15 patients.

Interim toxicity assessment was completed on the first 15 patients who completed the first two cycles of tri-modal therapy with no safety concerns noted.

12.2.6 Phase II Projected Accrual

It is estimated that the total accrual goal of 55 patients will be reached in approximately 24 months, with a treatment and follow-up period of approximately 18 months, making the entire study duration (including safety and efficacy assessments) approximately 50 months.

13. Laboratory and Pathology Correlative Studies

13.1 Correlative Studies: Mandatory Tumor and Peripheral Blood Samples

13.1.1 Tumoral Assessments

Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery, FFPE block (preferred) or a minimum of 15 unstained sections of 5 micron thickness plus 1 H&E slide. Sections should be cut with DNA precautions and mounted on plus charged slides. Analyses to be performed may include the following:

- PD-L1 expression (Ventana SP263 assay)
- Whole exome sequencing
- T cell receptor sequencing
- Gene expression by nanostring
- CD8 and other immunologic correlates by IHC

NOTE: Blocks must be less than 3 years old. If unstained slides are being submitted they must be less than 90 days old.

Submitted tumor samples should follow the below guidelines:

- Samples should be collected via a core needle of 18 gauge or larger or be collected as an excisional tumour biopsy sample. Where institutional practice in this setting uses a smaller gauge needle, samples should be submitted to ensure that availability of result can be achieved.
- The tumour specimen submitted should be of sufficient quantity (i.e., >100 tumour cells) to allow for PD-L1 immunohistochemistry analyses.
- When archival samples are used to assess PD-L1 status, the age of the sample / date of collection should be captured.
- Samples submitted for PD-L1 testing must be formalin fixed and embedded in paraffin.
- Samples from fine needle aspirates or bone metastasis are not appropriate for PD-L1 analysis.

13.1.2 Peripheral Blood Assessments

During Concurrent Therapy

Research bloods are to be drawn prior to treatment on C1D1, prior to treatment on C2D1, and prior to treatment on C5D1 during concurrent therapy or at time of confirmed progression IF confirmed progression occurs before Cycle 5, Day 1.

At each time point, collect one (1) 10 mL EDTA tube and two (2) 10 mL Streck tubes. **EDTA tube must be collected before the Streck tubes.**

Peripheral blood samples will be obtained for:

- Cytokine profiling (platform to be determined [TBD])
- ctDNA analysis
- T cell receptor repertoire analysis

13.1.3 Tumor Tissue and Peripheral Blood Analysis

Tumor tissue samples and Streck tubes will be sent ambient to John Hopkins University and processed EDTA tubes will be sent frozen to the ECOG-ACRIN Central Biorepository and Pathology Facility (EA CBPF).

Testing will be performed following receipt of accrued samples by John Hopkins

University. Any left-over samples will be stored for future analysis.

13.2 Assay Methodology

13.2.1 Tumor Tissue Studies

Baseline tumor will be obtained in all subjects. Archived tumor biopsies (core needle or excision) will be banked for future analysis.

The following studies may be performed depending on tissue quality and availability.

Immunohistochemical (IHC) staining. We will perform IHC of tumor samples to assess PD-L1 expression in tumor or tumor-infiltrating immune cells using the Ventana SP263 assay. Markers for further characterization of immune cell subsets (CD3, CD4, CD8, CD20, CD68, CD45RO), T regulatory cells-Treg (FOXP3) as well as other immune checkpoints (LAG3, TIM3) will be assessed. These additional assessments may be performed using multiplex IHC.

Whole exome sequencing to detect somatic genomic alterations. Using genome-wide methods we will perform whole-exome sequencing in pre-treatment tumors for identification of genomic correlates of response to durvalumab. Non-synonymous missense mutations identified will be used to predict mutant peptides and generate a neoantigen signature for each tumor using a computational pipeline we have developed.

T cell receptor sequencing. A separate targeted capture and sequencing analysis of the T cell receptor will be performed to assess T cell clonality.

Gene expression analyses. By nanostring or similar methods may also be performed.

13.2.2 Peripheral Blood Studies

Peripheral Blood Mononuclear Cells (PBMCs) will be obtained at time points indicated in Section 13.1.2. Samples will be banked for future analysis with plan to evaluate for immunologic markers of response and T cell receptor repertoire analysis.

ctDNA analysis will be performed on Streck tube samples at time points indicated in Section 13.1.2.

13.3 Pathology Sample Processing and Shipment

Sites should submit FFPE diagnosis tumor tissue block (preferred) or a minimum of 15 FFPE unstained, positively charged slides (2 sections per slide) plus H&E slide from a tumor tissue block within 3 months of patient registration. Thickness of the sections should be 5 micron and sections should be cut with DNA precautions.

Blocks must be less than 3 years old. If unstained slides are being submitted they must be less than 90 days old.

A copy of the pathology report from initial diagnosis should be sent when the sample is shipped. Samples should be shipped **Monday-Thursday**. Samples will be shipped ambient via overnight courier.

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Kits will be supplied. Instructions and shipping address will be provided.

13.4 Peripheral Blood Samples Processing and Shipment

13.4.1 Streck Tubes Processing

Fill tube completely. IMMEDIATELY mix the blood sample by gentle inversion 8-10 times (do not shake). One inversion is a complete turn of the wrist (180 degrees and back). Store at ambient temperature (15-30 degrees Celsius).

Streck tube should be shipped to the lab within 72 hours of collection via overnight courier at room temperature (Do NOT freeze. Proper insulation may be required for shipment during extreme temperature conditions). **NOTE:** Samples may be shipped on Friday for Monday delivery.

13.4.2 EDTA Tube Processing for Plasma and Buffy Coat

****Process sample within 30 minutes of collection****

- Gently mix blood sample by inversion 10 times (do not shake).
- Place tube immediately on wet ice for 5 minutes.
- Centrifuge at 1200 RPM for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RPM for 15 minutes). Immediately place the tube on wet ice after centrifugation.

After centrifugation, the plasma layer will be at the top half of the tube. The nucleated cells (WBC) will be in a whitish layer, called the “buffy coat”, just under the plasma and above the red blood cells.

Plasma Preparation:

- Using a transfer pipette take the top two-thirds of the plasma and transfer plasma into a 15 ml conical centrifuge tube, be careful not to disturb the buffy coat layer in the EDTA tube (**NOTE:** see below for buffy coat processing instructions). Centrifuge the 15 ml conical tube at 1200 RPM for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RPM for 15 minutes). Immediately place the conical tube on wet ice after centrifugation.
- Transfer equal amounts of plasma into two (2) properly labeled polypropylene tubes for cryopreservation being careful not to disturb the small PBMC/pellet.
- Store the two aliquots of plasma samples in the freezer at ≤ -70°C or colder until they are shipped to the ECOG-ACRIN Central Biorepository and Pathology Facility (EA CBPF).

Buffy Coat Preparation:

- From the EDTA tube remove and aliquot the “buffy coat”; be careful not to disturb the layer of red blood cells.
- Store the aliquot of cells in one (1) properly labeled polypropylene tube for cryopreservation.
- Store the sample in the freezer at ≤ -70°C or colder until it is shipped to the ECOG-ACRIN Central Biorepository and Pathology Facility (EA CBPF).

Plasma and buffy coat samples should be batched together and shipped approximately every 4 months. Individual patients should only be included in the shipment if all of their samples have been completed. Samples should be shipped **Monday-Thursday**. Samples must be shipped on dry ice via overnight courier.

Kits will be supplied. Instructions and shipping address will be provided.

14. Administrative

14.1 Protocol Compliance

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with, and be prepared by PrECOG and/or representatives. The Investigator should not implement any deviation or change to the protocol or consent without prior review and documented approval from PrECOG and/or representatives and the Institutional Review Board (IRB) of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

If a deviation or change to the approved protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, notification will be submitted to the IRB for review and approval as soon as possible afterward. Documentation of approval signed by the chairperson or designee of the IRB(s) should be in the study records. If PrECOG and/or representatives provides an amendment that substantially alters the study design or increases the potential risk to the patient; the consent form must be revised and submitted to the IRB(s) for review and approval; the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the Amendment; and the new form must be used to obtain consent from new patients prior to study entry. Information as to who investigators should send correspondence will be provided in additional study documents.

14.2 Institutional Review Board

Before study initiation, the Investigator must have written and dated approval from their respective IRB for the protocol, consent form, patient recruitment materials/process and any other written information to be provided to patients. The Investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, and any updates.

The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, amendments, and administrative letters) according to regulatory requirements, IRB or study site procedures.

14.3 Informed Consent Procedures

Investigators must ensure that patients who volunteer for clinical trials or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other information.

A protocol specific informed consent form (ICF) template will be provided to sites. Preparation of the site-specific consent form is the responsibility of the site Investigator and must include all applicable regulatory and IRB requirements, and must adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. All changes to the ICF template will be approved by PrECOG and/or their representatives prior to implementation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow PrECOG and/or its agents, regulatory authorities, and the IRB of record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in the informed consent form or other approved form obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted

the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the trial. The investigator is responsible for assuring adequate documentation of this process and for storage and maintenance of the original signed consent form for each patient/subject.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

14.4 Safety Communication

Investigators will be notified of all AEs that are serious, unexpected, and definitely, probably, or possibly related to the investigational product. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and submit a copy of this information to the IRB according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

14.5 Monitoring

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of investigational product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Monitoring of drug accountability will also occur.

The study may be evaluated by other auditors and government inspectors who must be allowed access to electronic Case Report Forms (eCRFs), source documents and other study files. The Investigator must notify PrECOG of any scheduled visits by regulatory authorities, and submit copies of all reports. Information as to who investigators should notify of an audit or where to address questions will be provided in additional study materials.

14.6 Study Records

An Investigator is required to maintain adequate regulatory files with corresponding communication and approvals, accurate histories, observations and other data on each individual treated. Full details of required regulatory documents will be provided in additional study materials. Data reported on the eCRFs must be consistent with the source documents as part of the patient record.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A study specific signature record will be maintained to document signatures and initials of all persons at a study site who are authorized to make entries and/or corrections on eCRFs as well as document other study-specific roles.

14.7 Electronic Case Report Form (eCRF) Information

Additional information regarding eCRF instructions, timelines for data entry/submission and query completion can be found in supplemental materials provided to the site. Sites will be expected to complete eCRFs as per the schedule provided and submit all relevant data as per the specified timelines. All items recorded on eCRFs must be found in source documents.

The completed eCRF must be promptly reviewed, electronically signed, and dated by the Principal Investigator.

Instructions for management of patients who do not receive any protocol therapy:

If a patient is registered and does not receive any assigned protocol treatment, baseline, Serious Adverse Event and follow-up data will still be entered and must be submitted according to the eCRF instructions. Document the reason for not starting protocol treatment on the appropriate electronic off treatment form.

14.8 Records Retention

FDA Regulations (21CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents for the periods described below for studies performed under a US Investigational New Drug (IND):

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

The Investigator must retain investigational product disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, whichever is longer. The Investigator must contact PrECOG and/or representatives prior to destroying any records associated with the study.

Information as to who investigators should contact for questions will be provided in additional study documents. PrECOG and/or representatives will notify the Investigator when the trial records for this study are no longer needed.

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Appendix I: ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix II: Cockcroft-Gault Formula

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [years]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

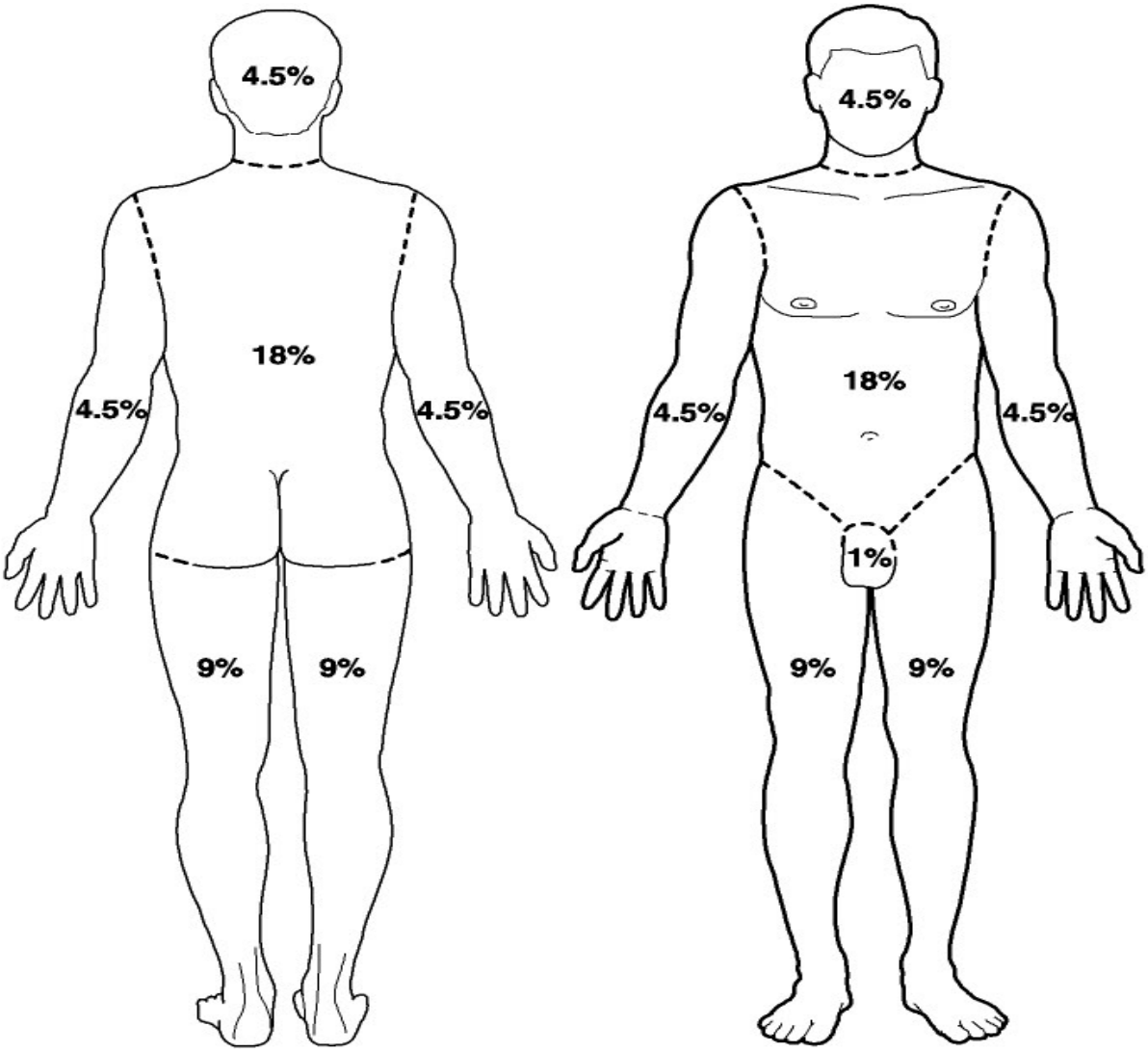
$$\text{Creatinine clearance for females} = \frac{(140 - \text{age [years]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})} \times 0.85$$

Source: Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992; 62:249

Appendix III: Rule of Nines

See the rule of nines as follows. Note that a patient's palm is approximately 1% total body surface area (TBSA) and can be used for estimating patchy areas.

- Head/neck - 9% TBSA
- Each arm - 9% TBSA
- Anterior thorax - 18% TBSA
- Posterior thorax - 18% TBSA
- Each leg - 18% TBSA
- Perineum - 1% TBSA



Source: http://my.firefighternation.com/forum/topics/889755:Topic:2902596?q=forum/topics/889755:Topic:2902596

Appendix IV: Investigator's Statement

1. I have carefully read this protocol entitled **"Open Label, Phase II Study of Anti-Programmed Death-Ligand 1 Antibody, Durvalumab (MEDI4736), in Combination with Chemotherapy for the First-Line Treatment of Unresectable Mesothelioma"**, **Version 5.0 dated 3/19/2018 (Protocol Number PrE0505)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.
2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.
3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.
4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.
5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from PrECOG, LLC unless this requirement is superseded by the FDA.

Principal Investigator (PI):

PI Name: _____

Site Name: _____

Signature of PI: _____

Date of Signature: _______________

MM DD YYYY