TITLE: A phase II clinical trial evaluating the safety and efficacy of durvalumab (MEDI4736) as 1st line therapy in advanced non-small cell lung cancer (NSCLC) patients with Eastern Cooperative Oncology Group (ECOG) performance status of 2

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SYNOPSIS

Rationale

Modulation of the immune checkpoints has permanently altered the therapeutic landscape of previously treated advanced NSCLC. PD1 inhibition with nivolumab is associated with overall response rates (ORRs) of about 20% in patients with advanced previously treated squamous and non-squamous NSCLC and, importantly, improves overall survival (OS) compared with docetaxel (Brahmer et al. 2015; Paz-Ares et al. 2015). Nivolumab is associated with less frequent treatment-related adverse events compared with docetaxel. In non-squamous NSCLC, 69% vs.88% of patients had events of any grade, and 10% vs. 54% had events of grade ≥ 3, respectively. Similarly, in squamous NSCLC, 58% vs. 86% had events of any grade, and 7% vs. 55% had events of grade ≥ 3, respectively (2% of docetaxel treated patients had events of grade 5). In advanced NSCLC patients, PD1 blockade with pembrolizumab is associated with an ORR of 19%, and a median duration of response (DOR) of 12.5 months. In patients with PD-L1 positive tumors (PD-L1 expression in ≥ 50% of cells in tumor nests or PD-L1+ bands in stroma as assessed by immunohistochemistry utilizing the Merck 22C3 antibody clone), the response rate is 45% (Garon et al. 2015).

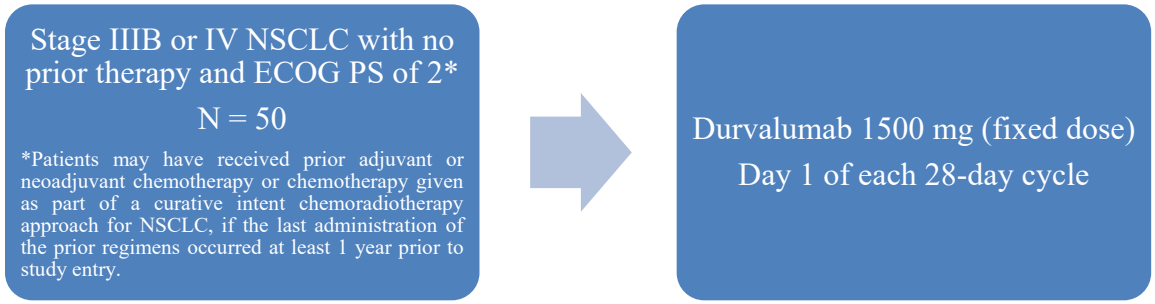
In an ongoing Phase 1/2, multicenter, open-label study evaluating the safety and clinical efficacy of the PD-L1 monoclonal antibody durvalumab 10 mg/kg IV every 2 weeks in patients with multiple solid tumor types including NSCLC, the ORR in NSCLC was 14% (23% in patients with PD-L1+ tumors by the SP263Ventana PD-L1 immunohistochemistry test), and the disease control rate (DCR) at 24 weeks was 24% (Rizvi et al. 2015). ORR was higher in squamous (21%) than in non-squamous patients (10%), and responses were durable. Drug-related adverse events (AEs) were reported in 48% of patients and were most frequently fatigue (14%), decreased appetite (9%), and nausea (8%). Grade ≥ 3 drug-related AEs were reported in 6% of patients. Recently, several phase I/II clinical trials have evaluated the clinical activity of monotherapy with PD1 and PD-L1 blocking antibodies in the 1st line treatment of advanced NSCLC. These clinical trials indicate early evidence of durable antitumor activity with response rates of 23-29% and tolerable toxicity profiles similar to what has been previously demonstrated with PD1 and PD-L1 checkpoint inhibition. There are currently several ongoing randomized phase III clinical trials evaluating PD1 and PD-L1 blocking antibodies in the 1st line treatment of advanced NSCLC. MYSTIC is a phase III open-label study of 1st line durvalumab (20 mg/kg IV every 4 weeks) with or without a monoclonal antibody to CTLA-4, tremelimumab (1 mg/kg IV every 4 weeks for up to 4 doses), vs. standard of care chemotherapy in advanced NSCLC (NCT02453282.) Notably, this clinical trial is being conducted in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

An ECOG performance status of 2 (PS2) is defined as being “ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours” (Oken et al. 1982). Up to 30 to 40% lung cancer patients present with an ECOG PS2 (Buccheri et al. 1996; Lilenbaum 2006). Performance status has long been recognized as an independent prognostic factor for survival, thus patients with a PS2 have typically been excluded from clinical trials in lung cancer (Stanley 1980; Brundage et al. 2002). More recent phase II and III clinical studies dedicated to defining the optimal therapeutic strategy in PS2 patients have

demonstrated a significant survival advantage with platinum-based doublet chemotherapy over single agent therapy with pemetrexed, paclitaxel or erlotinib in the 1st line treatment of advanced NSCLC (Lilenbaum et al. 2005; Lilenbaum et al. 2008; Zukin et al. 2013). Despite these data, platinum-based therapy in NSCLC patients with marginal performance status has not been universally adopted due to the perceived burden of excess toxicity associated with therapy (West 2013).

Study Design

This is a single-arm phase II clinical trial evaluating the safety and efficacy of the PD-L1 inhibitor durvalumab as first-line therapy in 50 patients with advanced NSCLC and ECOG PS2.



Hypothesis

We hypothesize that PD-L1 inhibition with durvalumab is a tolerable regimen with clinical activity in PS2 patients with advanced NSCLC.

Primary Objectives

- To estimate overall survival (OS) with durvalumab in advanced NSCLC patients with an ECOG PS2.
- To estimate the safety of durvalumab in NSCLC patients with PS2 as determined by grade ≥ 3treatment related adverse events.

Secondary Objectives

- To estimate the progression-free survival (PFS) with durvalumab in advanced NSCLC patients with PS2.
- To estimate overall response rate (ORR).
- To estimate the rate of 12-month survival (OS12).
- To estimate OS, PFS, and ORR by PD-L1 expression status
- To estimate the health related quality of life (HRQL) associated with durvalumab therapy in advanced NSCLC patients with PS 2.

Treatment Regimen

Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. Durvalumab will be administered at 1500 mg (fixed dose) q 4 weeks until disease progression, death, unacceptable toxicity or withdrawal of consent for a maximum of 12 months of therapy.

Statistical Methods

- ***Primary Objectives:***

    - The OS curve and a 90% confidence interval for the median OS will be estimated by standard methods (the Kaplan-Meier method for survival, and the Greenwood variance formula applied to log-transformed survival). Prior phase II/III clinical trials have demonstrated a median OS of about 5 months with single agent therapy in PS2 patients with advanced NSCLC (Lilenbaum et al. 2005; Lilenbaum et al. 2008; Zukin et al. 2013). A median OS of 9 months with durvalumab would demonstrate a clinically meaningful improvement over the historical control median OS of 5 months with single agent therapy. Assuming 18 months of accrual with 6 months of follow-up, N=50 patients would be required to have 85% power for a 90% confidence interval for median survival to exclude 5 months (and 78% power for a 95% confidence interval).

    - Safety will be summarized for all patients who receive at least one dose of study drug. All adverse events that are determined to be possibly, probably or definitely related to treatment will be tabulated according to grade and type, in order of frequency. Each adverse event will be counted only once per patient, with the highest grade recorded. Serious adverse events and adverse events of special interest (ASEI, defined in section 8.1.3) will also be tabulated by frequency. Listings will be provided for all on-study deaths and adverse events that lead to withdrawal from study. A rate of grade ≥3 treatment related adverse events of 30% or less would suggest that durvalumab is more tolerable than a platinum doublet in this population [Lilenbaum et al. 2008].

- ***Secondary Objectives:***

    - PFS will be evaluated using the same methodology as for OS. PFS and OS will be evaluated for all patients and for subgroups by PD-L1 status. The ORR and OS12 will be estimated with a 90% Wilson Score confidence interval, for all patients and based on PD-L1 status. HRQL at baseline, the end of each 4-week cycle, and at the end of therapy will be assessed using the FACT-L v4 questionnaire (Cella, 2007). Total scores and subscales will be summarized for each patient, and analyzed using standard linear mixed models methods and generalized estimating equations. The primary analysis will summarize baseline QOL, average change over the first two cycles of treatment, and average QOL in survivors at approximately 6 months and 12 months.

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
Cmax	peak concentration
Cmax,ss	peak concentration at steady state
Cmin	trough concentration
Cmin,ss	trough concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response

Abbreviation or special term	**Explanation**
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
FACT-L	Functional Assessment of Cancer Therapy – Lung
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IHC	immunohistochemistry
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody
MDSC	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life

Abbreviation or special term	Explanation
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
t½	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
Tmax	time to peak concentration
Tmax,ss	time to peak concentration at steady state
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
WFI	water for injection
WHO	World Health Organization

1. OBJECTIVES

1.1 Primary Objectives

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1.2 Secondary Objectives

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2. BACKGROUND

2.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer mortality in the United States and worldwide (Siegel et al. 2015). An estimated 221,200 new lung cancer cases will be diagnosed in 2015 in the United States alone, and 158,040 lung cancer deaths are estimated to occur (Siegel et al. 2015). A series of large randomized controlled phase III clinical trials established platinum-based doublets as the standard of care in the treatment of metastatic NSCLC with response rates of 20-30% and a median survival of 8-11 months (Fossella et al. 2003; Kelly et al. 2001; Scagliotti et al. 2002; Schiller et al. 2002; Zatloukal et al. 2203). In patients with newly diagnosed advanced NSCLC, cisplatin/pemetrexed and cisplatin/gemcitabine were associated with similar efficacy, though a histology specific survival benefit was noted in patients with non-squamous histology with pemetrexed-based therapy, while a survival detriment was noted in patients with squamous histology (Scagliotti et al. 2008). Bevacizumab, a monoclonal antibody to VEGF has been associated with a survival advantage in combination with carboplatin/paclitaxel compared with carboplatin/paclitaxel alone in patients with non-squamous NSCLC (Sandler et al. 2006).

Recent advances in the treatment of metastatic NSCLC have come from recognition that NSCLC is not a single disease entity, but rather a collection of distinct molecularly-driven neoplasms. Lynch et al. and Paez et al. first described a subset of patients with NSCLC harboring activating mutations in the *EGFR* gene who responded to treatment with EGFR tyrosine kinase inhibitors (TKIs) (Lynch et al. 2004; Paez et al. 2004). This discovery permanently shifted the landscape of NSCLC therapy to a personalized approach based on the molecular alterations of a patient's tumor; a paradigm typified not only by targeted therapies in EGFR mutant lung adenocarcinomas, but also in ALK translocation driven adenocarcinomas of the lung and more

recently, the therapeutic advances in lung adenocarcinomas harboring ROS1 gene rearrangements (Kwak et al. 2010; Bergethon et al. 2012; Shaw et al. 2014).

In the treatment of the majority of patients without an actionable oncogenic driver, modulation of the immune checkpoints has altered the therapeutic landscape of previously treated advanced NSCLC. PD1 inhibition with nivolumab is associated with overall response rates (ORRs) of about 20% in patients with advanced previously treated squamous and non-squamous NSCLC and, importantly, improves overall survival (OS) compared with docetaxel (Brahmer et al. 2015; Paz-Ares et al. 2015). Nivolumab is associated with less frequent treatment-related adverse events compared with docetaxel. In non-squamous NSCLC, 69% vs.88% of patients had events of any grade, and 10% vs. 54% had events of grade ≥ 3, respectively. Similarly, in squamous NSCLC, 58% vs. 86% had events of any grade, and 7% vs. 55% had events of grade ≥ 3, respectively (2% of docetaxel treated patients had events of grade 5). In advanced NSCLC patients, PD1 blockade with pembrolizumab is associated with an ORR of 19%, and a median duration of response (DOR) of 12.5 months. In patients with PD-L1 positive tumors (PD-L1 expression in ≥ 50% of cells in tumor nests or PD-L1+ bands in stroma as assessed by immunohistochemistry utilizing the Merck 22C3 antibody clone), the response rate is 45% (Garon et al. 2015).

2.2 Durvalumab

Investigators should be familiar with the current durvalumab Investigator Brochure (IB Version 9.0)

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (Mab) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

2.2.1 Summary of non-clinical experience

The non-clinical experience is fully described in the current version of the durvalumab Investigator's Brochure (IB Version 9.0)

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that durvalumab inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1

antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of durvalumab. Following intravenous (IV) administration, the PK of durvalumab in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life (t1/2) increased with increasing doses, suggesting saturable target binding-mediated clearance of durvalumab. No apparent gender differences in PK profiles were observed for durvalumab.

In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA: durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab.

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

2.2.2 Summary of clinical experience

Clinical experience with durvalumab is fully described in the current version of the durvalumab Investigator's Brochure (Version 9.0).

As of the DCO dates (15Apr2015 to 12Jul2015, Durvalumab IB Version 8.0), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer

agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

Pharmacokinetics and Product Metabolism

Study CD-ON-durvalumab-1108: As of 09 Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 μg/mL throughout the dosing interval.

As of 09 Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

Safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with durvalumab monotherapy in key clinical studies are described below.

Adverse Event Profile of Durvalumab Monotherapy

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07 May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%). Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were

dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

Efficacy

Study CD-ON-durvalumab-1108: Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Study D4190C00007: Of the 32 subjects with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 subjects had at least 1 post-baseline disease assessment. Among these subjects, the best overall responses were marrow complete remission (mCR) in 4 subjects (19.0%); stable disease (SD) in 4 subjects (19.0%); and progressive disease (PD) in 5 subjects (23.8%). The remaining 8 subjects (38.1%) did not meet the criteria for complete remission (CR), mCR, partial remission (PR), SD, or PD at the date of assessment.

Study CD-ON-durvalumab-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥ 12 weeks) was 79.4%.

Fixed Dosing

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

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

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (Appendix C).

2.3 Rationale

In an ongoing Phase 1/2, multicenter, open-label study evaluating the safety and clinical efficacy of the PD-L1 monoclonal antibody durvalumab 10 mg/kg IV every 2 weeks in patients with multiple solid tumor types including NSCLC, the ORR in NSCLC was 14% (23% in patients with PD-L1+ tumors by the SP263Ventana PD-L1 immunohistochemistry test), and the disease control rate (DCR) at 24 weeks was 24% (Rizvi et al. 2015). ORR was higher in squamous (21%) than in non-squamous patients (10%), and responses were durable. Drug-related adverse events (AEs) were reported in 48% of patients and were most frequently fatigue (14%), decreased appetite (9%), and nausea (8%). Grade ≥ 3 drug-related AEs were reported in 6% of patients. Recently, several phase I/II clinical trials have evaluated the clinical activity of monotherapy with PD1 and PD-L1 blocking antibodies in the 1st line treatment of advanced NSCLC. These clinical trials indicate early evidence of durable antitumor activity with response rates of 23-29% and tolerable toxicity profiles similar to what has been previously demonstrated. There are currently several ongoing randomized phase III clinical trials evaluating PD1 and PD-L1 blocking antibodies in the 1st line treatment of advanced NSCLC. MYSTIC is a phase III open-label study of 1st line durvalumab (20 mg/kg IV every 4 weeks) with or without a monoclonal antibody to CTLA-4, tremelimumab (1 mg/kg IV every 4 weeks for up to 4 doses), vs. standard of care chemotherapy in advanced NSCLC (NCT02453282.) Notably, this clinical

trial is being conducted in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

An ECOG performance status of 2 (PS2) is defined as being "ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours" (Oken et al. 1982). Up to 30 to 40% lung cancer patients present with an ECOG PS2 (Buccheri et al. 1996; Lilenbaum 2006). Performance status has long been recognized as an independent prognostic factor for survival, thus patients with a PS2 have typically been excluded from clinical trials in lung cancer (Stanley 1980; Brundage et al. 2002). More recent phase II and III clinical studies dedicated to defining the optimal therapeutic strategy in PS2 patients have demonstrated a significant survival advantage with platinum-based doublet chemotherapy over single agent therapy with pemetrexed, paclitaxel or erlotinib in the 1st line treatment of advanced NSCLC (Lilenbaum et al. 2005; Lilenbaum et al. 2008; Zukin et al. 2013). Despite these data, platinum-based therapy in NSCLC patients with marginal performance status has not been universally adopted due to the perceived burden of excess toxicity associated with therapy (West 2013).

This is a single-arm phase II clinical trial evaluating the safety and efficacy of the PD-L1 inhibitor durvalumab as first-line therapy in 50 patients with advanced NSCLC and ECOG PS2. We hypothesize that PD-L1 inhibition with durvalumab is a safe and tolerable regimen and associated with a survival advantage in PS2 patients with advanced NSCLC. The results of this clinical study may reframe the treatment paradigm of advanced NSCLC patients with a PS2 to focus on immune modulation.

3. PATIENT SELECTION

3.1 Inclusion Criteria

1. Written informed consent and any locally-required authorization (e.g., HIPAA) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations

2. Patients must have histologically or cytologically confirmed Stage IIIB or IV (American Joint Committee on Cancer, 7th edition; AJCC 7) non-small cell lung cancer.

3. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 12 for the evaluation of measurable disease.

4. Patients must have not have received any prior therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) for the treatment of stage IV NSCLC. Patients may have received prior adjuvant or neoadjuvant chemotherapy or chemotherapy given as part of a curative intent chemoradiotherapy approach for NSCLC, if the last administration of the prior regimens occurred at least 1 year prior to study entry.

5. Age ≥ 18 years at time of study entry.

   Because no dosing or adverse event data are currently available on the use of durvalumab in patients <18 years of age, children are excluded from this study.

6. ECOG performance status of 2 (Appendix A).

7. Life expectancy of greater than 12 weeks.

8. Tissue available (archived or fresh tumor biopsy) for the PD-L1 assay.

9. Patients must have normal organ and marrow function as defined below:

   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (> 1500 per mm3)
   - Hemoglobin ≥ 9.0 g/dL
   - Platelet count ≥ 100 x 109/L (>100,000 per mm^3)
   - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (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 only in consultation with their physician.
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
   - Serum creatinine CL>30 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}.$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

10. Female subjects must either be of non-reproductive potential (ie, 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.

11. The effects of durvalumab on the developing human fetus are unknown. For this reason and because immunomodulatory agents are potentially teratogenic, sexually active women of child-bearing potential and men must agree to use adequate contraception (2 methods of effective contraception from screening) from screening, for the duration of study participation, and for at least 90 days following the last infusion of durvalumab (Section 6.2); cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

12. Subject 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.

3.2 Exclusion Criteria

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrollment in the present study.

2. Participation in another clinical study with an investigational product for cancer during the last 12 months.

3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.

4. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids, in excess of prednisone 10 mg/d or equivalent.

5. Sensitizing mutations in *EGFR* or rearrangements in *ALK* or *ROS1*.

6. History of allergic reactions attributed to compounds of similar chemical or biologic composition to durvalumab.

7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids. Patients may be on systemic corticosteroids provided the dose does not exceed prednisone 10 mg/d or equivalent for 1 week prior to study drug administration.

8. Active autoimmune disease requiring systemic treatment within the past 2 years.
   NOTE: Subjects with autoimmune disease, such as vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

9. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

10. History of primary immunodeficiency.

11. History of allogeneic organ transplant.

12. 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 evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

13. Known history of previous clinical diagnosis of tuberculosis.

14. History of leptomeningeal carcinomatosis.

15. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.

16. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

17. Subjects with uncontrolled seizures.

18. Pregnant women are excluded from this study because durvalumab is associated with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with durvalumab, breastfeeding should be discontinued if the mother is treated with durvalumab.

19. Prior history of radiation pneumonitis.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally by the Study Coordinator.
Following registration, patients should begin protocol treatment within 5 days.
Issues that would cause treatment delays should be discussed with the Investigator. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the coordination team and the treating physician investigator, a patient will be entered on study. To register a patient, the research nurse or data manager must complete the eligibility/registration form and review the signed Informed Consent, and HIPAA authorization form.

To complete the registration process, the research nurse or data manager will:

- Verify the eligibility
- Register the patient on study
- Assign a patient accession number

5. STUDY PROCEDURES

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis and Section 11.

5.1 Screening Phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Verification of Informed Consent
- Review of eligibility criteria
- Medical and surgical, oncologic history and demographics, tobacco and alcohol use
- Complete physical exam
- ECOG Performance Status

- Vitals signs (temperature, blood pressure, pulse rate, respiratory rate), weight, pulse oximetry
- Verification of tumor biopsy
- Review of prior/concomitant medications
- Imaging by CT/MRI
- Adverse event/Serious adverse event assessment
- Clinical laboratory tests for:
    - Hematology (see Table below)
    - Clinical chemistry (see Table below)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - , Hepatitis B surface antigen, hepatitis C antibody and HIV serologies
    - Urinalysis (see Table below)

5.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments, section 11. Pre-menopausal female subjects of childbearing potential must have a negative urine hCG or serum βhCG checked within 24 hours of 1st durvalumab administration.

5.3 End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for subjects who have completed durvalumab treatment and achieved disease control, or have discontinued durvalumab due to toxicity in the absence of confirmed progressive disease are provided in APPENDIX E.

Assessments for subjects who have discontinued durvalumab treatment due to confirmed PD are presented in APPENDIX F.

5.4 Description of procedures

5.4.1 Medical history and physical examination, weight and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed on study days noted in the Schedule of Assessments.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

Vital signs (temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry) will be measured per institutional standard of care or as clinically indicated, as noted in the Schedule of Assessments.

5.4.2 Clinical Laboratory Tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments, Appendix E and Appendix F for the timepoints of each test):

- Coagulation parameters: Prothrombin time, activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
    - Serum beta-human chorionic gonadotropin (at screening and as clinically indicated during treatment)
- Thyroid Stimulating Hormone (TSH)
    - free T3 and free T4 only if TSH is abnormal
- Other laboratory tests
    - Hepatitis B surface antigen, hepatitis C antibody
    - HIV antibody

Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase

Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid

[a] If Total bilirubin is ≥2x ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
[b] At baseline and as clinically indicated

Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells with use of the high power field for red blood cells

6. TREATMENT PLAN

6.1 Durvalumab Administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	**Premedications / Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Durvalumab	N/A	** in 500 cc NS	IV over 60 minutes (±5 minutes)	Day 1	28 days (4 weeks)

** Dose calculation is based in patient weight at the time of each treatment. See section 6.1.1 for fixed dose information for subjects weighing greater than or equal to 30 kg and Appendix C for calculation of dose for subjects with weight of less than 30 kg.

Study drug preparation

For patients weighing ≥ 30 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) (based on an average body WT of 75 kg) should be prepared. For subjects <30 kg body weight, dose is determined using body mass, calculating the stock volume of durvalumab to achieve the accurate dose according to Appendix C.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager 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 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v)dextrose for IV infusion 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., 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.

Patient weight at baseline should be used for dosing calculations in patients ≤30 kg unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For patients <30kg, Calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose according to Appendix C.

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.

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.

Monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs per institutional standard of care or as clinically indicated, as noted in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

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. 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.

6.2 General Concomitant Medication and Supportive Care Guidelines

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 below.

Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than the protocol specified therapy.
2. Any 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).
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 (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Rescue Medications	
Rescue/supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc])	Should be used when necessary for all patients

Contraception

Females of childbearing potential who are sexually active with a nonsterilised male partner must use 2 methods of effective contraception (see below) from screening, and for at least 90 days following the last infusion of durvalumab; cessation of birth control after this point should be

discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see below) from screening and for 90 days after receipt of the final dose of investigational product.

Effective methods of contraception (two methods must be used)

Barrier Methods	**Intrauterine Device Methods**	**Hormonal Methods**
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Combined pill Minipill Patch

[a] This is also considered a hormonal method.

Blood donation

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

6.3 Patient Reported Outcomes for FACT-L

To ensure completion of the FACT-L questionnaires at the appropriate time-points, assigned research staff must adhere to the instructions in this section. The patient should complete the FACT-L questionnaires in clinic at the following times: at baseline, prior to the start of each cycle, and at the end of therapy.

Research staff should instruct the patient how to properly fill in the FACT-L questionnaire per the following instructions:

- All questionnaires must be completed prior to any other study procedures (baseline following informed consent) and before discussion of current disease status to avoid biasing the patient's responses to the questions.
- Provide a private environment for the patient to answer the questions.
- Provide sufficient time for the patient to complete the questionnaire at their own pace.
- Avoid assistance from relatives, friends or clinic staff to help the patient answer the questionnaires. However, if the patient is unable to read the questionnaire (due to vision impairment such as blindness or uncorrected vision, illiteracy), the questionnaires may be read out loud by trained clinic staff and responses recorded.
- When the patient completes the questionnaire, it should be handed back to the person responsible for the questionnaires, checking for completeness prior to initiating any other procedures.
- Only one answer should be recorded for each question.

6.4 Duration of Therapy

Treatment may continue for up to 12 months (maximum 12 doses) or until one of the criteria for durvalumab discontinuation is met.

Permanent discontinuation of durvalumab

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

- Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab
- Withdrawal of consent or lost to follow-up
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Pregnancy or intent to become pregnant
- Any AE that meets criteria for discontinuation as defined in Appendix D.
- Grade ≥ 3 infusion reaction
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits

- Initiation of alternative anticancer therapy including another investigational agent

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Appendix E or F, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone at months 2, 3, 4, 6, 8, 10, 12 after stopping treatment, and then every 2 months after that as an alternative.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

6.5 Duration of Follow Up

Patients will be followed for 12 months after discontinuation of study therapy or until death, whichever occurs first. Patients discontinuing study therapy for unacceptable adverse event(s) will be followed at least until resolution or stabilization of the adverse event (Appendix E).

At the discretion of the sponsor-investigator (or sponsor/investigator) the study may be closed prematurely.

6.6 Criteria for Removal from Study Therapy

Patients will be discontinued from study therapy when any of the criteria listed in Section 6.4 applies. The reason for study therapy discontinuation and the date of discontinuation must be documented in the Case Report Form.

7. DOSING DELAYS/DOSE MODIFICATIONS

For adverse events (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 (see

below).

- 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 (Appendix D).

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study.

Immune-mediated reactions/irAEs, also considered to be AESIs, are important risks of immune checkpoint inhibitors, and are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. irAEs observed with durvalumab include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk, particularly with durvalumab and tremelimumab combination therapy.

Other inflammatory responses with potential immune-mediated etiology reported with durvalumab and similar molecules include, but are not limited to, myocarditis, pericarditis, and uveitis. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of the above events of interests should be considered to be immune-related.

- 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 1, 2, and 3 of Appendix D, respectively.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in the IB version 9.0. All toxicities will be graded according to NCI CTCAE v4.03.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

8.1 Safety parameters

8.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6 (R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

8.1.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

8.1.3 Definition of adverse events of special interest (ASEI)

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 the sponsor. 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-related adverse event (irAE) 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 irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with durvalumab include:

- Colitis
- Pneumonitis
- 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, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Pemphigoid

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

8.1.4 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs (Topalian et al, NEJM 2012). 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 Appendix D.

8.1.5 Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). 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 Appendix D.

8.1.6 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). 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 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × 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 Appendix D.

Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN 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.

8.1.7 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 Appendix D.

8.1.8 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix D.

8.1.9 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 Appendix D.

8.1.10 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 Appendix D.

8.1.11 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 Appendix D.

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 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x 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 Assessment of safety parameters

8.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03.

The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a

nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

8.3 Recording of adverse and serious adverse events

Adverse events will be recorded using the Adverse Event form using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

AE (verbatim)
The date and time when the AE started and stopped
Changes in NCI CTCAE grade and the maximum CTC grade attained
Whether the AE is serious or not
Investigator causality rating against durvalumab (yes or no)
Action taken with regard to durvalumab
Outcome

In addition, the following variables will be collected for SAEs as applicable:

Date AE met criteria for serious AE
Date Investigator became aware of serious AE
AE is serious due to <<criteria>>
Date of hospitalization
Date of discharge
Probable cause of death
Date of death
Autopsy performed
Description of AE
Causality assessment in relation to Study procedure(s)

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.1 Study recording period and follow-up for adverse events and serious adverse event

Adverse events and serious adverse events will be recorded from administration of the first dose of durvalumab, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab) or until the initiation of alternative anticancer therapy.

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

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

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.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post study events

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study subjects after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

8.3.2 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time the first dose of durvalumab is taken through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator and/or sponsor must inform the FDA, via a departmental SAE form, of any serious and unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the departmental SAE form report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure

that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

All events meeting the definition of a serious adverse event should be reported according to the internal departmental SAE checklist and SAE form. Copies should be sent to:

1. Investigator and Sponsor*****
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.

***** A cover page should accompany the departmental SAE form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-15-11317)

***** Sponsor must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

*** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox*:*** [redacted]

1. Contact info. and reporting guidelines for any supporting entities per contract

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

8.3.3 **Reporting of deaths**

All deaths that occur during the study or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported as follows:

Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within **24 hours** (see Section 8.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

8.3.4 **Other events requiring reporting**

8.3.4.1 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 the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 8.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 8.3). 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 (See Section 8.3). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

8.3.4.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 8.1.6 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*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 8.3.2 for contact information), 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 the sponsor and AstraZeneca/MedImmune.

8.3.4.3 Pregnancy

Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. 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 the appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site 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.

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 monotherapy.

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.

9. PHARMACEUTICAL INFORMATION

9.1 Durvalumab

The Pharmaceutical Development R & D Supply Chain Management section of AstraZeneca/MedImmune will supply durvalumab to the investigator as a 500-mg vial solution for infusion after dilution.

9.1.1 Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. 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.

9.1.2 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

10. BIOMARKER STUDIES

10.1 Biomarker Studies

10.1.1 PD-L1 Testing

PD-L1 testing will be performed per standard of care analysis methods in a CLIA certified lab.

Tumor tissue sample collection for PD-L1 testing

- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.
- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen obtained is less than 3 years old. 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 should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis. Samples taken from malignant pleural effusions or other appropriate

cytological specimens are acceptable for interpretation of PD-L1 status, and if sufficient tumor cells are present to complete the analysis.

11. STUDY CALENDAR

Schedule of study assessments: Screening and Treatment Period (up to 12 months: maximum of 12 doses)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Pre-screening**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**			
			Baseline	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**
				(±3 days)	**(±7 days)**	
Written informed consent/assignment of subject identification number	X					
Physical examination[a]		X	X	X		
ECOG performance status		X	X	X		
Medical and surgical history; review previous treatments for NSCLC		X				
Demography and history of tobacco and alcohol use		X				
Vital signs	Per institutional standard of care or as clinically indicated					
Weight		X	X	X		
Formal verification of eligibility criteria		X				
Obtain archived or fresh tumour biopsy for PD-L1 assay (Section 10 further detail)		X				
Hematology[d]		X	X	X		
Liver enzyme panel[d]				X		

Schedule of study assessments: Screening and Treatment Period (up to 12 months: maximum of 12 doses)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Pre-screening**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**			
			Baseline	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**
				(±3 days)	**(±7 days)**	
Serum Chemistry (Comprehensive metabolic panel plus Mg, LDH, uric acid)[d]		X	X	X		
Amylase/Lipase[d]		X	X	X		
Creatinine clearance (calculated)[d]		X	X	As clinically indicated		
Thyroid function tests (TSH and fT3 and fT4)[e]		X	X	X		
Serum βhCG (check pregnancy status)[f]			X	As clinically indicated		
Urinalysis[g]		X	X	X		
Coagulation parameters[h]		X	As clinically indicted			
Hepatitis B, and C; HIV[i]		X				
Adverse event/serious adverse event assessment		X	X	All visits		
Concomitant medications		X	X	All visits		
Palliative radiotherapy		As clinically indicated				
Durvalumab administration (monotherapy)		X	X	X		
FACT-L[j]			X	X		
Tumor assessment (CT or MRI)[k]		X			X	

a. Full physical examination at baseline; targeted physical examination at other timepoints
b. Vital signs include temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry will be assessed per institutional standard of care or as clinically indicated.
d. Comprehensive metabolic panel includes the following: Na, K, CL, CO_2, urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, total bilirubin, AST, ALT, and alkaline phosphatase; and Mg, LDH, uric acid. Calculated creatinine clearance to confirm adequate renal function per Cockcroft-Gault formula (see Inclusion Criteria). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results must be available and

reviewed before commencing an infusion. Gamma glutamyltransferase (GGTP) tested at Screening, Day 1 and as clinically indicated.
e. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
f. Pre-menopausal female subjects of childbearing potential only. Must be checked within 24 hours of 1st durvalumab administration; see section 5.4.2.
g. Urinalysis performed at Screening, baseline Day 1, every 4 weeks and as clinically indicated.
h. Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.
i. Screening for serum hepatitis B surface antigen, hepatitis C antibody, and HIV antibody.
j. See Appendix B and Section 6.3.
k. CT (preferred) or MRI scans of the chest, abdomen, and other sites if clinically indicated, preferably with IV contrast, are collected during screening (for baseline) and as close to and prior to initiation of study treatment. Screening brain MRI (preferably with IV contrast; or CT head with contrast in patients who are unable to have an MRI) to rule out metastasis requiring concurrent treatment. Timing of on-treatment (follow-up) CT/MRI scans is every 8 weeks (± 1 week) for the first 48 weeks and then at least every 12 weeks (± 1 week) until PD or off-study. Response according to RECIST 1.1 criteria (CR, PR) requires a confirmatory scan preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of CR, PR, or SD. A confirmation of progression scan is required for patients who are deemed clinically stable by the Investigator. The confirmatory scan is acquired preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of PD.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. 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 the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with durvalumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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.

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being

followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm 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.

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.

Conventional 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.

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.

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.

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 complete response (CR) or surgical resection is an endpoint.

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. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (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 stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters 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. (Note: the appearance of one or more new lesions is also considered progressions).

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

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions 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.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment

until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13. DATA REPORTING / REGULATORY REQUIREMENTS

13.1 Data Safety Monitoring Plan

Sponsor/Investigator, Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the DSMB meetings are available to anyone unable to attend the center DSMB.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

13.2 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and Guidelines on Good Clinical Practice compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Investigator (i.e., the study site principal investigator) and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

13.3 Data Handling and Record-Keeping

The Investigator (i.e., the study site principal investigator) will maintain records in accordance with Good Clinical Practice.

The investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

13.4 Institutional Review Board (IRB) Approval

The investigator (i.e., the study site principal investigator) will obtain, from the University of

Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice.

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of an sponsor's decision to modify the previously accepted clinical protocol, the sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or AE; or the dropping of a test intended to monitor the safety of the investigational drug.

13.5 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and University of Pittsburgh Medical Center, Commonwealth of Pennsylvania, and applicable federal agencies.

13.6 Informed Consent

The investigator (i.e., the study site principal investigator) will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the sponsor, will obtain the written, signed

informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator or sub-investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study. When a reconsent is required, the lead study coordinator will notify all sub-investigators and study coordinators via email that a reconsent is needed. The email notification will also list the changes in the new consent and specify which patients need to be reconsented.

14. STATISTICAL CONSIDERATIONS

14.1 Rationale for study design and sample size

Although platinum-based doublet chemotherapy demonstrates a survival advantage over single agent therapy with pemetrexed, paclitaxel or erlotinib in the 1st line treatment of advanced NSCLC with ECOG PS2 (Lilenbaum et al. 2005; Lilenbaum et al. 2008; Zukin et al. 2013), it has not been universally adopted due to the perceived burden of excess toxicity associated with therapy (West 2013). Our study investigates a possible therapy to address the unmet need of an effective, tolerable first-line therapy for the large population of advanced NSCLC patients with PS2. Durvalumab is in the class of PD-L1 monoclonal antibodies that have yielded durable responses in a sizeable minority of patients, without the side effects of a platinum doublet. A single-arm trial is appropriate given the development stage of durvalumab and the incremental steps required toward staging a much larger trial, such as to assess noninferiority with a platinum-based doublet. The trials cited above in this patient population establish benchmarks for reasonable and unreasonable efficacy and toxicity.

Prior phase II/III clinical trials have demonstrated a median OS of about 5 months with single agent therapy in PS2 patients with advanced NSCLC (Lilenbaum et al. 2005; Lilenbaum et al. 2008; Zukin et al. 2013). A median OS of 9 months with durvalumab (approximately the level achieved by the platinum-based doublets in these trials) would demonstrate a clinically meaningful improvement over the historical control median OS of 5 months with single agent therapy. Assuming 18 months of accrual with 6 months of follow-up, N=50 patients are required to have 85% power for a 90% confidence interval for median survival to exclude 5 months (and 78% power for a 95% confidence interval).

14.2 Analysis cohorts

The safety cohort includes all patients who receive at least one dose of study drug. (SAEs

occurring following written informed consent but before initiating study therapy will be reported as described in Section 8.3.2, but will not be part of study summaries.)

The primary efficacy cohort may exclude patients who withdraw from study therapy prior to the second cycle for reasons unrelated to disease progression or toxicity. Examples include patients who withdraw due to concerns about insurance coverage, or reluctance to travel an additional distance for study participation. However, these patients will be followed for overall survival if they do not withdraw consent, and will be included in a sensitivity analysis of efficacy endpoints for the full safety cohort.

14.3 Analysis plan

Summary tables describing the patient cohort will be compiled, including:

- Demographics (age, sex, race, ethnicity, smoking history, recent weight loss)
- Disease history (current stage, tumor sites, histology)
- Comorbidities at start of therapy (cardiac, pulmonary, other)
- PD-L1 expression status

Analysis of primary endpoints:

- The OS curve, median OS, and a 90% confidence interval for the median OS will be estimated by standard methods (the Kaplan-Meier method for survival, and the Greenwood variance formula applied to log-transformed survival) in the efficacy cohort (primary analysis) and safety cohort (sensitivity analysis). Durvalumab will be considered a promising therapy in this population if the estimated median OS is 9 months or greater, and/or the lower bound of a 90% confidence interval for the median OS is greater than 5 months. However, these results will be interpreted in the context of safety data and the presence of durable responses attributed to study therapy.).
- All adverse events that are determined to be possibly, probably or definitely related to treatment will be tabulated according to grade and type, in order of frequency in the safety cohort. Each adverse event will be counted only once per patient, with the highest grade recorded. Serious adverse events and adverse events of special interest (ASEI, defined in section 8.1.3) will also be tabulated by frequency. Listings will be provided for all on-study deaths and adverse events that lead to withdrawal from study.

  Lilenbaum et al (2008) observed a rate of grade ≥3 adverse events of 41% (90% CI 31%-53%) for a platinum-based doublet, and 27% (90% CI 18%-38%) for erlotinib. In this context of balancing expected toxicity and efficacy, a rate of grade ≥3 treatment related adverse events of 30% or less would be acceptable, especially if associated with efficacy in individuals. In a cohort of n=50, a 30% rate of grade ≥3 adverse events would have a 90% CI of (21%-41%), demonstrating it is likely more tolerable than the platinum doublet.

Secondary Objectives:

- PFS will be evaluated using the same methodology as for OS. PFS and OS will be evaluated in the unselected populations and based on PD-L1 status. The ORR and OS12 will be estimated with a 90% Wilson Score confidence interval, for the unselected population and based on PD-L1 status. HRQL at baseline, the end of each cycle, and at the end of therapy will be assessed using the FACT-L questionnaire (David Cella, Ph.D., 2007). Total scores and subscales will be summarized for each patient, and analyzed using standard linear mixed models methods and generalized estimating equations. The primary analysis will summarize baseline QOL, average changes over the first two cycles of treatment, and average QOL in survivors at approximately 6 months and 12 months.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: FACT-L (VERSION 4)

Assessment Date: _ _/_ _ /_ _ _ _
mm/dd/yyyy

FACT-L (v4) Worksheet **Protocol**: 16-054

Patient Initials: _ _ _ **Patient number**: _ _ _

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Assessment Date: _ _/_ _/_ _ _ _
mm/dd/yyyy

FACT-L (v4) Worksheet **Protocol:** 16-054

Patient Initials: _ _ _ **Patient number:** _ _ _

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Assessment Date: _ _/_ _ /_ _ _ _
mm/dd/yyyy

FACT-L (v4) Worksheet **Protocol**: 16-054

Patient Initials: _ _ _ **Patient number**: _ _ _

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

APPENDIX C: DURVALUMAB DOSE CALCULATIONS

Durvalumab Dosing

The durvalumab dosing should be done depending on subject weight (if subject is < 30kg):

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL).

Dose adjustments for each cycle only needed for greater than 10% change in weight.

5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10 (mL/vial)

Example:

1. Cohort dose: 10 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 300 mg = 10 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 300 mg / 50 (mg/mL) = 6.0 mL

5. The theoretical number of vials required for dose preparation:

Number of vials = 6.0 (mL) / 10.0 (mL/vial) = 1 vials

APPENDIX D: DOSING DELAYS/DOSE MODIFICATIONS

<table>
<tr><th colspan="4">Table 1- Immune-Mediated Reactions</th></tr>
<tr><th></th><th colspan="2">Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td rowspan="4">Immune-related Adverse Events (Overall Management For toxicities not noted below)</td><td colspan="2">Drug administration modifications of study drug/study regimen will be made to manage potential immune-related 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.</td><td rowspan="4">It is recommended that management of irAEs follow the guidelines presented in this table:
− Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.)
− In the absence of a clear alternative etiology, all events should be considered potentially immune related.
− Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events
− For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent
− If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (> 28 days of taper)
− More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids.
− Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this</td></tr>
<tr><td>Grade 1</td><td>No dose modification</td></tr>
<tr><td>Grade 2</td><td>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</td></tr>
</table>

		may require prolonged or continued steroid replacement 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, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	situation should be based upon a benefit/risk analysis for that patient
	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		

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
Pneumonitis/ ILD	Grade of Pneumonitis (CTCAE version 4.03)	Any Grade	– 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

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
			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 at next	For Grade 2 (Mild to Moderate New Symptoms) − Monitor symptoms daily and consider hospitalization − Promptly start systemic steroids (e.g., prednisone 1-2mg/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 to 4mg/kg/day started − If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/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

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
		scheduled treatment date will be based upon treating physician's clinical judgment and after completion of steroid taper.	≥28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation) - Consider pulmonary and infectious disease consult - Consider as necessary discussing with study physician
	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 - 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 5mg/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 PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[1]

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	Any Grade	– 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)	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 2 diarrhea (stool frequency of 4-6 over baseline per day)	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	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 or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day 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

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
		drug/study regimen can be resumed after completion of steroid taper.	methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult 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 PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	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 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/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 PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis**	Grade of Liver Function Test Elevation (CTCAE version 4.03)	Any Grade	− Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin (TB) − Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1 (AST or ALT > ULN to 3 times ULN and/or TB > ULN to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	For Grade 1 AST or ALT and/or TB elevation - Continue LFT monitoring per protocol
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times 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	For Grade 2 AST or ALT and or TB 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, discuss with study physician. − If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day or IV equivalent. − If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. − If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[1] . Discuss with study physician if

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
		completion of steroid taper.	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 PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × 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	For Grade 3 or 4 AST or ALT and/or TB 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 (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 PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
		elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause	

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade		- 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 creatinine 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; >1.5X-3.0XULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 •If toxicity worsens then treat as Grade	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

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
		3 or Grade 4 •If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. - Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP 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 > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	- 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 or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin	Grade of Skin Rash (Please refer	Any Grade	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
formations)	to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash)		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 If toxicity improves to ≤ Grade 1 or baseline, then resume study drug/study regimen after completion of steroid taper	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 - 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, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent - Consider skin biopsy if persistent for >1-2 weeks or recurs

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
	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] - 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 PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)		- Consult Endocrinologist - 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, hypotension and weakness. - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.)

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
			- Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. - 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 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) - Monitor patient with appropriate endocrine function tests - 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 endocrinology consult.
	Grade 2 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism, 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	For Grade 2: (including those with symptomatic endocrinopathy) - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Initiate hormone replacement as needed for management - Evaluate endocrine function, and as clinically indicated, consider pituitary scan - For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). - - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
		event stabilizes and 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) the event stabilizes and is controlled, 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	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.

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Resume study drug/study regimen once event stabilizes and after completion of steroid taper	For Grade 3 or 4: - Consult endocrinologist - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - Administer hormone replacement therapy as necessary. - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity - Once improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - Discuss with study physician
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any Grade		- 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,

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
			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	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 stabilizes to grade ≤1 and after completion of steroid taper	- Discuss 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 1-2mg/kg/day or IV equivalent - If no improvement within 3-5 days despite 1-2mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IV IG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue Study	For Grade 3 or 4: - Discuss with study physician - Obtain Neurology Consult - Consider hospitalization - Promptly initiate empiric IV methylprednisolone 1 to 2

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
		drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	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
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		Any Grade	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which 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

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
			(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 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 IV IG and followed by plasmapheresis if not responsive to IV IG
	Grade 1	No dose modification	− Discuss 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 unless the symptoms are very minor and stable
	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 − Discuss 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. Important to consider

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
			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 IV IG. 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. Patients requiring treatment should be started with IV IG and followed by

Table 1- Immune-Mediated Reactions (continued)			
		Dose Modifications	**Toxicity Management**
			plasmapheresis if not responsive to IV IG.
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study drug/study regimen if Grade 3 irAE 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: - Discuss with study physician - Recommend hospitalization - Monitor symptoms and obtain neurological consult *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 IV IG. 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*: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG
	Grade 4	Permanently discontinue study drug/study regimen	

Table 2- Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		- Management per institutional standard at the discretion of investigator - Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event.	For Grade 1 or Grade 2: - Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator - Consider premedication per institutional standard prior to subsequent doses - Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Table 3- Non-immune Mediated Reactions		
CTC Grade/Severity	**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

Table 3- Non-immune Mediated Reactions		
CTC Grade/Severity	**Dose Modification**	**Toxicity Management**
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 at next scheduled dose. 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 the sponsor)	Treat accordingly as per institutional standard

Abbreviations:
AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

APPENDIX E
Schedule of study procedures: follow-up for subjects who have completed durvalumab treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued durvalumab due to toxicity in the absence of confirmed progression of disease

Evaluation	**Time Since Last Dose of durvalumab**							
	Day (±3)	**Months (±1 week)**						**12 Months, then Every 6 Months thereafter (±2 weeks)**
	30	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	Per institutional standard of care or as clinically indicated							
Weight	X							
Serum βhCG	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
ECOG performance status	X	X	X		X (and month 9)			X
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					X
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[b]	X							
FACT-L questionnaire	X		X	For subjects who achieve disease control following 12 months of treatment, patient questionnaires should be completed every 12 weeks relative to the date of enrollment until confirmed PD by RECIST 1.1 by investigational site review. For subjects who discontinue study drug due to toxicity or a reason other than confirmed PD, patient questionnaires should be completed relative to the date of enrollment as follows: every 8 weeks for the first 12 months, then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review.					

APPENDIX E
Schedule of study procedures: follow-up for subjects who have completed durvalumab treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued durvalumab due to toxicity in the absence of confirmed progression of disease

Evaluation	**Time Since Last Dose of durvalumab**							
	Day (±3)	**Months (±1 week)**						**12 Months, then Every 6 Months thereafter (±2 weeks)**
	30	**2**	**3**	**4**	**6**	**8**	**10**	
Tumor assessment (CT or MRI)	For subjects who achieve disease control following 12 months of treatment, tumor assessments should be performed every 12 weeks (± 1 week) relative to the date of first infusion thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Assessments for timings of confirmatory scans. For subjects who discontinue durvalumab due to toxicity (or symptomatic deterioration), tumor assessments should be performed relative to the date of first infusion as follows: every 8 weeks (± 1 week) for the first 48 weeks (per Schedule of Assessments), then every 12 weeks(± 1 week) until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Assessments for timings of confirmatory scans. Upon confirmed PD, scans should be conducted according to local standard clinical practice until a new treatment is started (these scans are optional).							

a. Full physical exam
b. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

APPENDIX F
Schedule of study procedures: follow-up for subjects who have discontinued durvalumab treatment due to confirmed progression of disease at the discretion of the investigator

Evaluation	**Time Since Last Dose of durvalumab**							
	Day (±3)	**Months (±1 week)**						**12 Months, then Every 6 Months thereafter (±2 weeks)**
	30	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	Per institutional standard of care or as clinically indicated.							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
ECOG performance status[b]	X	X	X					
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Serum βhCG	X							
Hematology	X	X	X					
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[c]	X							
FACT-L questionnaire	X		X					
Tumor assessment (CT or MRI)	For subjects who continue on durvalumab post-confirmed progression at the investigator's discretion (following consultation with the sponsor), tumor assessments should be performed relative to the date of first infusion per Schedule of Assessments until durvalumab is stopped. For subjects who discontinue durvalumab following confirmed progression, scans should be conducted according to local clinical practice until a new treatment is started (these scans are optional).							

a. Full physical exam
b. PS to be collected if available at the 2 monthly calls to obtain subsequent anti-cancer therapy and survival status
c. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.