Investigational Drugs	Durvalumab (MEDI4736) Tremelimumab
Substance(s)	
Study Number	ESR-14-10531/WINSHIP3112-15
Version Number	3.1
Date	May 24, 2018

IND #: 129242
Cross-Reference IND #: 010096; 112249

A randomized study of tremelimumab plus durvalumab combination with or without radiation in relapsed small cell lung cancer

Study Sponsor:	Taofeek K. Owonikoko, MD, PhD, MSCR
Principal Investigator:	Taofeek K. Owonikoko, MD, PhD, MSCR
Co-Investigators	Suresh Ramalingam, MD
	Dong M. Shin, MD
	Nabil F. Saba, MD
	Suchita Pakkala, MD
	Rathi Pillai, MD
	Gabriel L. Sica, MD, PhD
	Kristin Higgins, MD
	Jonathan Beitler, MD
	Walter J. Curran, MD
	Ned Waller, MD, PhD
	Conor Steuer, MD
	William Small, MD
Study Statistician	Zhengjia Chen, PhD
Research Assistant	Guojing Zhang, MS
	Ernestine Mahar

SUMMARY OF CHANGES IN THE AMENDMENTS TO PROTOCOL V. 2.0, MAY 9, 2016

Page xviii: Update list of appendix

Page 26: Include section 4.5 to provide detailed instructions for registration procedures and study ID number

Page 33: Correct formatting errors in section 6

Page 71: In section 8.3.3, replace blue tiger topped tubes with purple topped EDTA bottles and update the amount of blood required from 10mls to 30mls for cfDNA analysis

Page 72: Update table to provide specific instructions in the summary of schedule of sample collection for pharmacodynamic analysis

Page 129: Include Appendix 7 with details of sample processing for cfDNA assay

SUMMARY OF CHANGES IN THE AMENDMENT TO PROTOCOL V. 3.0, SEPTEMBER 16, 2016

Page 36: Update Table l per MEDI4736 Treme Toxicity Management dated 8-19-2016

SUMMARY OF CHANGES IN THE AMENDMENT TO PROTOCOL V. 3.1, MAY 24, 2018

Page 124: Re-included Appendix 7 with details of sample processing for cfDNA assay

PROTOCOL SYNOPSIS

Clinical Protocol ESR-14-10531/WINSHIP3112-15

Study Title: A randomized study of tremelimumab plus durvalumab combination with or without radiation in relapsed small cell lung cancer
Protocol Number: ESR-14-10531/Winship3112-15
Clinical Phase: 2
Study Duration: 36 months
Investigational Product(s) and Reference Therapy: • Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. • Tremelimumab is supplied as a sterile solution for IV infusion, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL, accounting to 400 mg/vial) of tremelimumab, in an isotonic solution at pH 5.5.
Research Hypothesis 1. Immune checkpoint therapy will be efficacious and will confer meaningful clinical benefit in relapsed SCLC 2. Priming with XRT prior to immune checkpoint treatment will result in enhanced clinical efficacy of immune checkpoint modulators in relapsed SCLC
Objectives: **Primary Objectives:** To compare the efficacy (PFS and ORR) of combined immune checkpoint inhibitor therapy with or without radiation as treatment for relapsed SCLC **Secondary Objective(s)**: Assess the impact of antigen priming using XRT on the efficacy of immune checkpoint inhibitors Determine the overall survival (OS) associated with this treatment strategy in relapsed SCLC **Exploratory Objective(s):** Characterize tumor infiltrating lymphocytes (TILs) and PD-L1/PD1 expression in paired tumor biopsies at baseline, end of cycle 2 and at the time of progression. Determine dynamic changes in cell free DNA(cfDNA) and the immunophenotype of peripheral blood repertoire of circulating lymphocytes using multiparameter flow cytometry Determine changes in circulating cytokine mediators of inflammation and immunity using Luminex assay
Study Design:

Randomized 2-arm, single stage study design. Arm I: Durvalumab + Tremelimumab Arm II: Radiation followed by Durvalumab + Tremelimumab
Number of Centers: 1
Number of Subjects: 20 (10 patients per Arm of study)
Study Population: Relapsed SCLC patients

Inclusion Criteria:

- Histology or cytology confirmed diagnosis of small cell lung cancer
- Previously treated with a platinum doublet and not more than 2 prior lines of therapy
- Written informed consent and any locally-required authorization (e.g.,) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
- Age $\geq$ 18 years at time of study entry
- Eastern Cooperative Oncology Group (ECOG performance status of 0 or 2
- Adequate normal organ and marrow function as defined below:
- Haemoglobin $\geq$ 9.0 g/dL
- Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L ($\geq$ 1500 per mm^3)
- Platelet count $\geq$ 100 x 10^9/L ($\geq$100,000 per mm^3)
- Serum bilirubin $\leq$ 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) $\leq$ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be $\leq$ 5x ULN
- Serum creatinine CL>40 mL/min by the Cockcroft-Gault or MDRD formula or by 24-hour urine collection for determination of creatinine clearance:
- Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: $\geq$60 years old and no menses for $\geq$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.

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.

Exclusion Criteria:

- Any previous treatment with a PD1, PD-L1 or CTLA4 inhibitor
- Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, Tumor embolization, monoclonal antibodies, other investigational agent) $\leq$ *14* days prior to the first dose of study drug ($\leq$ *7* days (five half-lives) prior to the first dose of study drug for subjects who have received prior oral TKIs and within 6 weeks for nitrosourea or mitomycin C).
- Mean QT interval corrected for heart rate (QTc) $\geq$470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction
- Current or prior use of immunosuppressive medication within 28 days before the first dose of Durvalumab or Tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid
- Any unresolved toxicity (>CTCAE grade 2) from previous anti-cancer therapy. *Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy)*
- Any prior Grade $\geq$3 immune-related adverse event (irAE) while receiving any previous

immunotherapy agent, or any unresolved irAE >Grade 1

- Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency
- History of allogeneic organ transplant
- History of hypersensitivity to Tremelimumab, MEDI4736 or any excipient
- 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
- Known history of previous clinical diagnosis of tuberculosis
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving Durvalumab or tremelimumab
- Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are unwilling to employ an effective method of birth control
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
- Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
- Subjects with uncontrolled seizures.
- Patients may not be receiving any other investigational agents or non-investigational agents administered with the purpose of controlling cancer growth (Use of conventional external beam radiation therapy will be allowed during protocol therapy solely for palliation of localised painful lesions or bone lesions at risk of fracture provided the radiation field does not encompass any selected target lesions required for assessment).
- Patients with uncontrolled symptomatic brain metastases.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Patients who require ongoing treatment with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
- Patient is unable or unwilling to abide by the study protocol or cooperate fully with the investigator

see Section 4.2 for durvalumab-specific and tremelimumab requirements

Investigational Product(s), Dose, and Mode of Administration:

Durvalumab, 1500 mg Q4W (equivalent to 20 mg/kg Q4W) for 12 months in patients > 30 kg

Tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W) for up to 4 doses/cycles in patients >30 kg

Weight-based dosing should be utilized for patients <30 kg durvalumab 20 mg/kg Q4 and tremelimumab 1 mg/kg Q4

Standard Treatment:

Priming XRT (Arm II only) up to 30Gy in 1 week

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Safety and toxicity will be assessed and graded using CTCAE v. 4.0

Patient reported outcome assessed using FACT-L questionnaire

Efficacy Assessments:

Primary:

i. Progression free survival (PFS)

PFS will be measured from time of enrolment until objective disease progression or death

ii. Objective response rate

Objective response (ORR, DoR, DCR) will be assessed using cross sectional imaging and categorized according to RECIST 1.1 criteria

Secondary:

i. Immune related objective response rate
ii. Overall survival

Exploratory:

Pharmacodynamic / Pharmacokinetic Assessments (if applicable):

i. Immunophenotype of TILs and peripheral circulating lymphocyte
ii. Changes in circulating (cfDNA)
iii. PD-L1 expression in paired tumor biopsy following treatment using the Ventana assay
iv. Tumor infiltrating lymphocytes (TILs) repertoire and PD-L1/PD1 expression in tumor biopsies collected at:

a. Baseline

b. End of cycle 2

c. At progression.

v. Dynamic changes in (cfDNA) and the immunophenotype of peripheral blood repertoire of circulating lymphocytes using multiparameter flow cytometry

Changes in circulating cytokine mediators of inflammation, type I and type II immune response using Luminex assay

Statistical Methods and Data Analysis:

Data on patient demographics, tumor characteristics, response rate and pharmacodynamic (PD) biomarkers will be summarized using descriptive statistics.

Randomization by blocked randomization at the end of screening for all eligible patients

OS and PFS time will be analyzed using Kaplan Meier method

Inferential statistics will be employed to correlate PD biomarkers and efficacy outcome. Two-sided paired t-test will be used to compare biomarkers expressions between pre and post treatment samples. ANOVA and Kruskal-Wallis tests will be used to compare the degree of biomarker changes between the treatment groups. The proportion of patients with objective response will be estimated with exact 95% confidence intervals. Changes in pharmacodynamic endpoints will be correlated with response using Fisher exact test.

All analysis will be performed using SAS software version 9.3.

Sample Size Determination:

For sample size determination, efficacy comparison was based on historical data with topotecan. Assuming a median PFS of 3 months if the intervention is no better than the historical PFS associated with topotecan based on the PFS from two recent randomized phase III studies of topotecan (Evans et al., 2015),(von Pawel et al., 2014) and a promising median PFS of 7 months if the investigational treatment is superior (based on the duration of response recorded in a phase II study of combined PD-1 and CTLA-4 blockade in relapsed SCLC), 10 patients treated in each arm of the study will provide 87% power to demonstrate the hypothesized efficacy improvement at a 1-sided 10% alpha level test.

Similarly, with the same sample size of 10 patients in each arm, we will have 64% power at a 1-sided alpha of 10% to demonstrate a promising response rate of 30% for the investigational therapy versus the historical response rate of 10% with topotecan in the same patient population. Assuming an observed response rate of 30% (3 out of 10 patients) the 95% exact confidence interval of the response rate will be [6.7%, 65.2%] and 90% exact confidence internal of the response rate will be [8.7%, 60.7%].

SCHEDULE OF STUDY ASSESSMENTS

Schedule of study assessments: Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)	**Screening period**	**Radiation window**	**All assessments to be performed pre-infusion unless stated otherwise**				
			Baseline assessment	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-21 to -7**	**-7 to -1**	**1**	**Day 1 of the week**			
Week	**-3 to -2**	**-1**	**1**	**3, 5, 7, 9, 11, 13, etc.**	**5, 9, 13, 17, 21, etc.**	**9, 17, 25, 33, 41 and 49**	**13, 25, 37, 49**
				(±3 days)		**(±7 days)**	
Written informed consent/assignment of subject identification number	X						
Fresh Tumor biopsy	X					X[k]	
Eligibility Verification and Randomization	X						
Medical history	X						
Hepatitis B and C; HIV	X						
Urine hCG or serum βhCG[b]	X		As clinically applicable				
Durvalumab administration[$]			X		X		
Tremelimumab[$]			X		X		
Physical examination[c]	X		X		X		
Vital signs (pre- during and post-infusion vital signs assessments)[d]	X		X		X		
Pre-treatments XRT (Arm II only)		X					
Electrocardiogram[e]	X		X			X (week 9 only)	
Adverse event/serious adverse event assessment[l]		X	X	All visits			
Concomitant medications	X		X	All visits			

Schedule of study assessments: Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)	**Screening period**	**Radiation window**	**All assessments to be performed pre-infusion unless stated otherwise**				
			Baseline assessment	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-21 to -7**	**-7 to -1**	**1**	**Day 1 of the week**			
Week	**-3 to -2**	**-1**	**1**	**3, 5, 7, 9, 11, 13, etc.**	**5, 9, 13, 17, 21, etc.**	**9, 17, 25, 33, 41 and 49**	**13, 25, 37, 49**
				(±3 days)		**(±7 days)**	
Palliative radiotherapy				As clinically indicated for symptomatic non target lesions			
Liver enzyme panel[f]	X		X		X		
Serum Chemistry (complete clin chem. panel including Liver enzymes)[f]	X		X		X		
Thyroid function tests (TSH and fT3 and fT4)[g]	X		X		X		
Hematology[f]	X	X	X		X		
Urinalysis[h]	X				X		
Coagulation parameters[i]	X	As clinically indicted					
Plasma sample for cfDNA, circulating immune mediating cytokines and chemokines[a]		X		X	~~X~~	X	
Peripheral blood for FACS [a]		X		Week 3	Week 5	Week 9	
Patient questionnaires[#]		X			Week 5 only	X	
Tumor assessment (CT or MRI) [j]	X					X	X

[a] Sample collection at baseline, (end of XRT for Arm II patients), at C1D15 week, C2D1; C3D1 and at progression

[b] Pre-menopausal female subjects of childbearing potential only; urine or serum test allowed for screening but only serum pregnancy test allowed while on treatment.

[c] Full physical examination at baseline; targeted physical examination at other time points

[d] Subjects will have their vital signs (blood pressure and pulse) measured before, during and after the infusion at the following times (based on a 60-minute infusion):

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

  If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

e Baseline ECG on C1D1 and on treatment ECG on C3D1 (Week 9). ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion.

f See section 8.2.5 for list of labs. If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

g 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.

h Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

i Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

j Timing of CT scans: default is every 8 weeks for the first 6 months and then every 12 weeks until confirmed PD.

k collect fresh tumor biopsy at the end of cycle 2 and at the time of confirmed disease progression

l For AEs/SAEs reported during prescreening additional information such as medical history and concomitant medications may be needed.

$: Concurrent administration Q 4 weeks for four doses thereafter continue durvalumab alone Q4 weeks (total of 1 year or until treatment discontinuation).

#: Functional Assessment of Cancer Therapy - Lung (FACT-L) questionnaire

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement

Abbreviation or special term	Explanation
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E

Abbreviation or special term	Explanation
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease

Abbreviation or special term	Explanation
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine

Abbreviation or special term	Explanation
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Disease Background

SCLC is one of the most lethal cancers with more than 20,000 newly diagnosed patients in the US in 2014 (Siegel et al., 2014). More than 80% of these patients die from their disease within 2 years of diagnosis and less than 5% of patients are alive at 5 years (Owonikoko et al., 2007). There has not been any meaningful improvement in the survival of SCLC patients in the past 3 decades (Behera et al., 2014). Although the majority of SCLC patients (70%) will respond to frontline chemotherapy, there is a near universal recurrence of disease, which is oftentimes resistant to further treatment leading to early death (Pillai and Owonikoko, 2014). The relapsed disease setting therefore represents the area of greatest unmet need for novel treatments in SCLC. Different strategies to improve outcomes following relapse have met with limited success (Owonikoko et al., 2012). Indeed, single agent topotecan remains the only approved treatment for relapsed SCLC more than 2 decades after its initial approval based on toxicity profile rather than superior efficacy compared to conventional multi-agent chemotherapy (Schiller et al., 2001; Schiller et al., 1996). While the use of targeted biologic agents has led to astounding success in the treatment of non-small cell lung cancer (Shaw et al., 2013a; Shaw et al., 2013b) novel approaches have not been successful to date in SCLC.

Tumor-Directed Immunity and SCLC

SCLC patients with paraneoplastic syndrome achieve prolonged and durable disease control in contrast to patients without paraneoplastic syndrome in the setting of SCLC diagnosis (Maddison et al., 1999; Tani et al., 2008). Also, high levels of suppressor T-reg and low effector T cells were observed in the peripheral circulation of patients with extensive stage (SCLC-ED) and limited stage small cell lung cancer (SCLC-LD) who progress following frontline therapy. Similarly, a high ratio of effector cells to T-regs was associated with improved survival in SCLC-LD (Koyama et al., 2008). Recent data indicates potential benefit of immune checkpoint inhibitors in SCLC where phased, (but not concurrent) administration of ipilimumab, an anti-CTLA4 antibody, with chemotherapy demonstrated improved efficacy in SCLC-ED (Reck et al., 2013).

Limited institutional experience and large randomized studies also suggest survival benefit of XRT in SCLC-ED (Ben J. Slotman, 2014; Guy C. Jones, 2014). Moreover, XRT can induce PD-L1 expression on Tumor and stromal cells along with increase in myeloid-derived suppressor cells (MDSCs) in preclinical models (Deng et al., 2014a; Deng et al., 2014b). Furthermore, the release of Tumor-associated antigens following cell death induced by XRT may be highly immunogenic (Deng et al., 2014a; Deng et al., 2014b), leading to potent

abscopal effect at distant Tumor sites (Blanquicett et al., 2005). The combination of an anti-PD-L1 inhibitor and XRT was also synergistic in xenograft models of pancreatic, colon and breast cancer (Blanquicett et al., 2005; Deng et al., 2014a; Deng et al., 2014b).

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

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

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. T cells play a critical role in antitumor immunity and their infiltration and activity have been linked to improved prognosis in a number of cancers (Pagès et al, 2010; Nakano et al, 2001; Suzuki et al, 2011; Burt et al, 2011). Immune evasion, primarily through suppression of T-cell activity, is now recognized as one of the hallmarks of cancer. Such evasion can occur via a range of mechanisms including production of suppressive cytokines such as IL-10, secretion of chemokines and growth factors that recruit and sustain suppressive regulatory T cells (Tregs) and inflammatory macrophages, and expression of inhibitory surface molecules such as B7-H1. Tumor types characterized as being responsive to immunotherapy-based approaches include melanoma (Weber et al, 2012), renal cell carcinoma (RCC; McDermott, 2009), bladder cancer (Kresowik and Griffith, 2009), and malignant mesothelioma (Bograd et al, 2011). Inhibition of CTLA-4 signaling is a validated approach to cancer therapy, as shown by the approval in 2011 of

ipilimumab for the treatment of metastatic melanoma based on statistically significant and clinically meaningful improvement in OS (Hodi et al, 2010; Robert et al, 2011).

In general, tumor response rates to anti-CTLA-4 therapy are low (~10%). However, in patients who respond, the responses are generally durable, lasting several months even in patients with aggressive tumors such as refractory metastatic melanoma. Because these agents work through activation of the immune system and not by directly targeting the tumor, responses can occur late and some patients may have perceived progression of their disease in advance of developing disease stabilization or a tumor response. In some cases, early growth of pre-existing lesions or the appearance of new lesions may have been due to immune-cell infiltration into the tumor and not due to proliferation and extension of neoplastic cells, per se (Wolchok et al, 2009). Overall, although the impact on conventionally-defined PFS can be small, durable response or stable disease seen in a proportion of patients can lead to significant prolongation of OS. The melanoma data with ipilimumab clearly demonstrate that a small proportion of patients with an objective response had significant prolongation of OS, supporting the development of this class of agents in other tumors. Although Phase 2 and Phase 3 studies of tremelimumab in metastatic melanoma did not meet the primary endpoints of response rate and OS, respectively, the data suggest activity of tremelimumab in melanoma (Kirkwood et al, 2010; Ribas et al, 2013). In a large Phase 3 randomized study comparing tremelimumab with dacarbazine (DTIC)/temozolomide in patients with advanced melanoma, the reported median OS in the final analysis was 12.58 months for tremelimumab versus 10.71 months for DTIC/temozolomide (HR = 1.1416, p = 0.1272; Ribas et al, 2013).

Immune checkpoint inhibitor therapy in relapsed SCLC

There is limited experience with checkpoint inhibitors in relapsed SCLC compared to NSCLC where this class of agents is now an approved standard of care option. Preliminary results of early phase clinical trials of anti PD-1 and anti PD-L1 inhibitors in SCLC showed strong promise. IN KEYNOTE-028 study, pembrolizumab was tested in relapsed SCLC patients who have failed standard therapy. Pembrolizumab (10 mg/kg) was given every 2 weeks for up to 2 year or until confirmed progression or unacceptable toxicity. A total of 157 patients with SCLC were screened of which 42 (29%) had PD-L1+ tumors (defined as >1% staining). Twenty patients were treated with pembrolizumab (55% men; median age, 59 y; 75% ECOG PS 1). All 20 treated patients received prior platinum and etoposide. Grade 3-5 adverse events were Asthenia (5%), elevated bilirubin (5%) and colitis (5%). Seven of 20 (35%) evaluable patients had a partial response; one (5%) patient had stable disease while the remaining patients either had progressive disease (9; 45%) or had not yet had an assessment performed (3; 15%). The time to response was 8.6 weeks (7.7-16.1 weeks) and responses were durable, with all responders on treatment for 16+ weeks (Ott et al., 2015).

CHECKMATE 032 was a phase I/II trial that studied nivolumab, anti PD-1 antibody as a single agent and in combination with ipilimumab, an antibody targeting CTLA4. The study enrolled 128 patients (regardless of PD-L1 expression) and assign them to nivolumab alone (3mg/kg Q3W); nivolumab (1mg/kg Q3W) plus ipilimumab (1mg/kg Q3W); nivolumab (1mg/kg Q3W) plus ipilimumab (3mg/kg Q3W) and nivolumab (3mg/kg Q3W) plus ipilimumab (1mg/kg Q3W). After four cycles of treatment, all patients continued with single agent nivolumab (3mg/kg Q2W). Pooled data from 90 patients treated with single agent (40 patients) or combination (50 patients) showed intriguing signal of efficacy especially for the combination. The median age was 63 and 65 in both groups respectively with approximately 35% with platinum refractory disease. Treatment-related adverse events were uncommon (7.5% versus 11%) and treatment-related death in a patient treated with the combination. The response rate was 18% and 32% respectively and disease control rate of 38 and 54% in the single agent nivolumab and combination groups respectively. The median duration of response was not yet reached (4.1; 11+) for the Nivolumab single agent arm and 6.9 months (1.5; 11.1+) for the combination arm. The median OS was 4.4 (2.9, 9.4) months versus 8.2 (3.7, NR) months in the single agent and the combination groups respectively (Antonia et al., 2015).

1.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors. This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-H1 (programmed cell death ligand 1 [PD-L1]).

1.1.2 Durvalumab

The non-clinical and clinical experience is fully described in the current version of the durvalumab Investigator's Brochure (IB Version 8.0).

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1.

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of patients with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of patients with tumors lacking PD-L1 (Mu et al 2011). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of several non-clinical studies using mouse tumor models support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity (Hirano et al 2005, Iwai et al 2002).

Durvalumab has been given to humans as part of ongoing studies as a single drug or in combination with other drugs 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.

As of 09Feb2015, 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 $\geq$ 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 $\geq$ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab $\geq$ 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 $\geq$ 40 µg/mL throughout the dosing interval.

As of 09Feb2015, 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.

1.1.3 Tremelimumab

The non-clinical and clinical experience is fully described in the current version of the tremelimumab Investigator's Brochure (IB Version 5.0). Tremelimumab is an IgG 2 kappa isotype mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) also known as CD152 (cluster of differentiation 152) This is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures. In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. (Refer to the tremelimumab IB, Edition 5.0, for more information.) Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cut-off date of 12 November 2014 (for all studies except D4190C00006, which has a cut-off date of 4 December 2014), 973 patients have received tremelimumab monotherapy (not including 497 patients who have been treated in the blinded Phase 2b study, D4880C00003) and 208 patients have received tremelimumab in combination with other agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.4.2.2. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.6 for guidance on management of tremelimumab-related toxicities.

Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22 days. Overall, a low incidence of ADAs (<6%) was observed for treatment with tremelimumab.

1.1.4 Durvalumab in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity because the mechanisms of action of CTLA-4 and PD-1 are non-redundant; therefore, AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/PDx, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

Study D4190C00006: As of 20Feb2015, durvalumab PK (n = 55) and tremelimumab PK (n = 26) data were available from 10 cohorts (1a, 2a, 3a, 3b, 4, 4a, 5, 5a, 8, and 9) following durvalumab every 4 weeks (Q4W) or Q2W dosing in combination with tremelimumab Q4W regimens. An approximately dose-proportional increase in PK exposure (C_{max} and area under the concentration-time curve from 0 to 28 days [AUC_{0-28}]) of both durvalumab and tremelimumab was observed over the dose range of 3 to 15 mg/kg durvalumab Q4W and 1 to 10 mg/kg tremelimumab Q4W. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. It is to be noted that steady state PK parameters are based on limited numbers of subjects. The observed PK exposures of durvalumab and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

As of 20Feb2015, ADA data were available from 60 subjects for durvalumab and 53 subjects for tremelimumab in Study D4190C00006. Four of 60 subjects were ADA positive for anti-durvalumab antibodies post treatment. One of 53 subjects was ADA positive for anti-tremelimumab antibodies post treatment. There was no clear relationship between ADA and the dose of either durvalumab or tremelimumab, and no obvious association between ADA and safety or efficacy.

Durvalumab has also been combined with other anticancer agents, including gefitinib, dabrafenib, and trametinib. To date, no PK interaction has been observed between durvalumab and these agents.

1.2 Research hypothesis

1. Immune checkpoint therapy will be efficacious and will confer meaningful clinical benefit in relapsed SCLC

2. Concomitant immune checkpoint treatment with XRT will enhance the clinical efficacy of immune checkpoint modulators in relapsed SCLC

1.3 Rationale for conducting this study

SCLC patients with paraneoplastic syndrome achieve prolonged and durable disease control in contrast to patients without paraneoplastic syndrome in the setting of SCLC diagnosis. (10,

11) Also, high levels of suppressor T-reg and low effector T cells were observed in the peripheral circulation of patients with extensive stage (SCLC-ED) and limited stage small cell lung cancer (SCLC-LD) who progress following frontline therapy. Similarly, a high ratio of effector cells to T-regs was associated with improved survival in SCLC-LD. (12) Recent data indicates potential benefit of immune checkpoint inhibitors in SCLC where phased, (but not concurrent) administration of ipilimumab, an anti-CTLA4 antibody, with chemotherapy demonstrated improved efficacy in SCLC-ED.(13) Preliminary report of studies of PD-1 pathway targeted therapy showed reliable signal of activity in relapsed SCLC. Moreover, the combination of a CTLA-4 and PD-1 pathway targeting agents showed greater benefit over single agent. Nonetheless, only a third of patients derived significant benefit from this combination therapy strategy. The incorporation of a complementary intervention likely to further enhance immune checkpoint therapy without increasing the risk of toxicity is likely to further extend the benefit of immune checkpoint inhibitors to a greater proportion of SCLC patients. Emerging data indicates efficacy of immune checkpoint inhibitors in SCLC including published data from the study of pembrolizumab and nivolumab in relapsed SCLC. However, the efficacy impact in unselected patients appears somewhat modest thereby calling for strategies to both identify patients likely to benefit and to further enhance the efficacy of the treatment.

Limited institutional experience and large randomized studies also suggest survival benefit of XRT in SCLC-ED (Ben J. Slotman, 2014; Guy C. Jones, 2014). Moreover, XRT can induce PD-L1 expression on tumor and stromal cells along with increase in myeloid-derived suppressor cells (MDSCs) in preclinical models (Deng et al., 2014a; Deng et al., 2014b). Furthermore, the release of tumor-associated antigens following cell death induced by XRT may be highly immunogenic (Deng et al., 2014a; Deng et al., 2014b), leading to potent abscopal effect at distant tumor sites (Blanquicett et al., 2005). The combination of an anti-PD-L1 inhibitor and XRT was also synergistic in xenograft models of pancreatic, colon and breast cancer (Blanquicett et al., 2005; Deng et al., 2014a; Deng et al., 2014b).

The biologic premise behind the strategy of combining immune modulating agent and XRT is the expectation that the tumor-antigen release achieved by localized radiation will activate tumor specific adaptive immune response, which can be further enhanced by systemic immune-stimulating agents. Thus, XRT is able to induce local tumor response at the site of XRT delivery but also at distant sites through the abscopal effect phenomenon, whereby localized radiation results in immune-mediated tumor regression in disease sites well outside of the radiation field (Tang et al., 2014). This study will also allow us to demonstrate the safety of the combination of irradiation along with combined immune checkpoint blockade.

As an antibody that blocks the interaction between PD-L1 and its receptors, durvalumab may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile (Brahmer et al 2012,). Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In

addition, durvalumab monotherapy has shown durable responses in NSCLC in Study 1108 (see Section 1.4.1.1).

The rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity (). In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable. Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC, with further updated details presented in this clinical study protocol.
The current study will test whether combined immune checkpoint along with or without XRT will confer greater benefit over immune checkpoint therapy alone in relapsed SCLC. The study design also allows the assessment of the safety of the combination of irradiation along with combined immune checkpoint blockade.

1.3.1 Durvalumab + tremelimumab combination therapy dose rationale

The durvalumab + tremelimumab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

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

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

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

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

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

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

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of

11 patients in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR), 1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD). (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

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

1.3.2 Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up.

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis (Hodi et al 2014, Brahmer et al 2014, Drake et al 2013). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis.

MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported (Herbst et al 2013).

Similar long term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1 antibodies such as durvalumab, or the combination of the two.

1.4 Benefit/risk and ethical assessment

Patients with relapsed SCLC have limited therapeutic options. Topotecan is the only approved therapy in this setting and is associated with a meager response rate of ~10% in unselected patients. The combination of inhibitors targeting PD1 and CTLA4 signaling pathways have been established to be safe. Moreover, this combination appears quite promising in early phase testing with response rate of >30%. Therefore, the risk-benefit balance is positive overall for the proposed study.

1.4.1 Potential benefits

1.4.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Data from Study 1108 were presented at the European Society for Medical Oncology 2014 Congress. 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%). (Antonia et al 2014b).

1.4.1.2 Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an RR of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis; Korn et al 2008) were observed (Kirkwood et al 2010). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed

an RR of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant . Additionally, a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who had responded or remained stable failed to achieve statistical significance. The primary endpoint of PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

1.4.1.3 Durvalumab + tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.1.4 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma. Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab in Study D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

Current experience with single-agent IMT studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. To date, no assay has been established or validated, and no single approach has proven accurate, for patient enrichment for IMTs. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor infiltrating cells may be associated with greater clinical benefit.

Data from ongoing studies with durvalumab and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (e.g., NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious (in terms of ORR) in patients who are PD-L1-positive.

Given these findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1–positive tumors. There is also an unmet medical need in patients with PD-L1–negative tumors that needs to be addressed. Data, as of 27 January 2015 from Study 006 show that with the addition of tremelimumab to durvalumab, the ORR can be increased to 25% in patients with PD-L1 negative NSCLC. As patients with PD-L1 positive disease can also have an increase in ORR, from 25% with durvalumab monotherapy, to 36%

with the combination of durvalumab and tremelimumab, the study will enroll all patients with NSCLC, with an emphasis on those determined to be PD-L1 negative.

1.4.2 Potential risks

1.4.2.1 Durvalumab

Potential risks, based on the mechanism of action of durvalumab and related molecules, include immune-mediated reactions, such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy or neurologic events. Additional important potential risks include infusion-related reactions, hypersensitivity, anaphylaxis or serious allergic reactions, serious infections, and immune complex disease.

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 07May2015, 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.

1.4.2.2 Tremelimumab

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated gastrointestinal (GI) events including enterocolitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; hepatitis including autoimmune hepatitis and increased serum ALT and AST; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratory tract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the data cutoff date of 12 November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014 and not including 497 patients who have been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product (IP), and deaths.

1.4.2.3 Durvalumab + tremelimumab

No safety studies in animals have been performed combining tremelimumab with durvalumab. As both CTLA-4 and PD-L1 have mechanisms of actions that enhance activation of immune cells, their potential to induce cytokine release was tested in a whole-blood assay system. Durvalumab and tremelimumab, either alone or in combination, did not induce cytokine release in blood from any donor.

Study D4190C00006: The safety profile of durvalumab and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjects treated with Durvalumab and tremelimumab combination therapy (not including subjects treated with blinded investigational product). As of 15Apr2015, 95 of 102 subjects (93.1%) reported at least 1 AE. All subjects in the

tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; subjects in the durvalumab 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest AE rate (77.8%). Treatment-related AEs were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjects being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each), rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related ≥ Grade 3 AEs reported in ≥ 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment-related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase in 2 subjects; myasthenia gravis in 1 subject; and pericardial effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the MEDI4736 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported SAEs, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty-six subjects (35.3%) experienced treatment-related SAEs. Twenty-seven subjects (26.5%) permanently discontinued treatment due to AEs. Treatment-related AEs resulting in discontinuation in ≥ 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3 subjects), and increased AST (2 subjects).Additional safety results from this study are presented in Section 1.3.1 and the durvalumab IB.

In the literature, using the combination of the same class of drugs (e.g., anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of AEs assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with Grade 3 or 4 events assessed by the Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment-related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment-related in the combination therapy included hepatic events (in 15% of patients), GI events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

1.4.2.4 Fixed Dosing for durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed

dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (*N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma*) [Wang et al. 2014]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others [Ng 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) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Fixed dosing of durvalumab and tremelimumab 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.

2. STUDY OBJECTIVE

2.1.1 Primary objective(s)

To assess the efficacy (PFS and ORR) of combined immune checkpoint inhibitor therapy as treatment for relapsed SCLC

2.1.2 Secondary objective(s)

Assess the impact of antigen priming using XRT on the efficacy of immune checkpoint inhibitors

Determine immune related objective response rate

Estimate overall survival measured as time from randomization to death from any cause

2.1.3 Exploratory objective(s)

Characterize tumor infiltrating lymphocytes (TILs) and PD-L1/PD1 expression in paired tumor biopsies at baseline, end of cycle 2 and at the time of progression.

Determine dynamic changes in cell free DNA (cfDNA) and the immunophenotype of peripheral blood repertoire of circulating lymphocytes using multiparameter flow cytometry

Determine changes in circulating cytokine mediators of inflammation and immunity using Luminex assay

3. STUDY DESIGN

3.1 Overview of study design

This is a prospective, proof-of-concept, 2-cohort clinical trial in relapsed SCLC. Consenting patients who have failed frontline platinum-based chemotherapy, with good performance status (0-2 on ECOG scale) and adequate end-organ function will be enrolled. Ten patients will be enrolled in Arm I and will be treated with Durvalumab and Tremelimumab combination every 4 weeks for 4 doses followed by single agent Durvalumab every 4 weeks for up to 1 year or until disease progression. Arm II patients will first undergo XRT (up to 30Gy in 3-5 fractions) to a known site of disease involvement prior to starting systemic treatment. This will be followed by systemic therapy similar to Arm I consisting of Durvalumab and Tremelimumab combination for 4 doses and then single agent Durvalumab for up to 1 year or until disease progression with tremelimumab and Durvalumab. Patients who continue to derive benefit from treatment with the Durvalumab/Tremelimumab combination may be allowed to continue treatment with single agent durvalumab for up to 2 years in the absence of intolerable toxicity or disease progression.

This design enables us to assess the clinical efficacy of combined immune checkpoint treatment (Arm I and II pooled); to establish the safety of sequential combination of immune checkpoint inhibitors and XRT (Arm II) and also to explore the priming effect of XRT on immune checkpoint therapy (Arm I vs II).

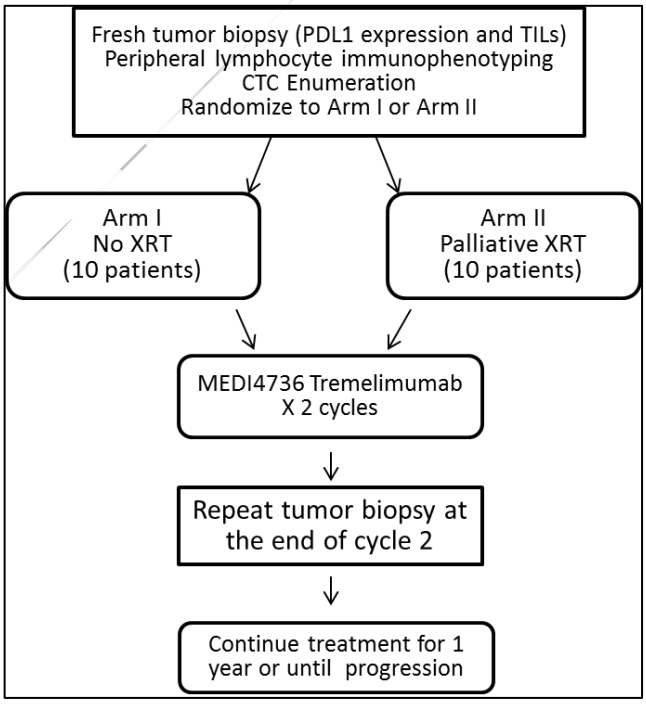
All enrolled patients will have a baseline plasma sample for circulating tumor free DNA (ctfDNA) to measure disease burden and antigen release, as well as a tumor biopsy for assessment of PD-L1 expression and to characterize the phenotype of the tumor infiltrating lymphocytes (TILs). A repeat ctfDNA sample will be collected at the end of radiation treatment (Arm II only). Repeat tumor biopsy will be obtained at the end of cycle 2 for all patients in both arms of the study. These samples will be employed to characterize the same endpoints of tumor burden, PD-L1 expression and TILs with comparison of immune cell repertoire between responding and non responding patients.

Treatment with durvalumab will continue for up to 1 year in the absence of toxicity or disease progression in all patients. Treatment may be extended for another year if continuing clinical benefit in the patient and there are no safety concerns.

Restaging scans will be obtained after every 2 cycles of therapy (for the first 6 months) and every 3 cycles thereafter.

3.2 Study schema

Figure 1. ***Study flow chart***



3.3 Study Oversight for Safety Evaluation

The study may be stopped if, in the judgment of the Sponsor or the Winship Data Safety Monitoring Committee (DSMC), study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

In terminating the study, adequate consideration will be given to the protection of the patients' interests.

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Under no circumstances will there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Written informed consent and any locally-required authorization (e.g.,) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
2. Age $\geq$ 18 years at time of study entry
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
4. Adequate normal organ and marrow function as defined below:
   - Haemoglobin $\geq$ 9.0 g/dL
   - Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L ($\geq$ 1500 per mm^3)
   - Platelet count $\geq$ 100 x 10^9/L ($\geq$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>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

  Males:

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

  Females:

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

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

6. 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.

7. Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria.

8. Patients must have histologically or cytologically confirmed small cell lung cancer

9. Patients must have measurable disease, defined as at least one lesion (excluding the lesion for palliative XRT) 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. See Section 9 for the evaluation of measurable disease.

10. Patient must have failed or found to be intolerant of standard frontline platinum-based regimens and must not have received > 2 prior lines of therapy (NB: Retreatment with a platinum-based doublet for sensitive relapse counts as another line therapy; however substitution of cisplatin with carboplatin or vice versa due to toxicity does not count as a separate regimen).

11. Negative urine or serum pregnancy test within 48 hours before starting study treatment in women with childbearing potential

12. Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Previous enrolment *or randomization* in the present study

3. Treatment with an investigational product during the last *2 weeks*

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

5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 14 days prior to the first dose of study drug (≤ 7 days or four half-lives, whichever is longer, prior to the first dose of study drug for subjects who have received prior TKIs [e.g., erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C).

6. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction

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

8. Any unresolved toxicity (>CTCAE grade <<2>>) from previous anti-cancer therapy. *Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy)*

9. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1

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

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

12. History of primary immunodeficiency

13. History of allogeneic organ transplant

14. History of hypersensitivity to durvalumab or any excipient

15. History of hypersensitivity to the combination or comparator agent

16. 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

17. Known history of previous clinical diagnosis of tuberculosis

18. History of leptomeningeal carcinomatosis

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

20. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control

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

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

23. Subjects with uncontrolled seizures.

24. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period

25. Patients receiving any other investigational agents for any reason or non-investigational agents administered for the purpose of controlling cancer growth (Use of conventional external beam radiation therapy will be allowed during protocol therapy solely for palliation of localised painful lesions or bone lesions at risk of fracture provided the radiation field does not encompass any selected target lesions required for assessment).

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of study treatment

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

1. Withdrawal of consent or lost to follow-up

2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing

3. 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

4. Pregnancy or intent to become pregnant

5. Any AE that meets criteria for discontinuation as defined in Section 6.6.

6. Grade ≥ 3 infusion reaction

7. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits

8. Initiation of alternative anticancer therapy including another investigational agent

9. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab + tremelimumab

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 Section 10.0 and Appendix 1 or 2, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled I 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 every 3 months as an alternative.

Withdrawal of consent

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

4.4 Replacement of subjects

Eligible patients who come off study not due to disease progression prior to undergoing the first restaging scan will be replaced.

4.5 Subject Registration

Eligible patients will be entered sequentially as identified by the investigators. To register a patient, the following documents should be obtained and confirmed by the Study Coordinator:

- Copy of required laboratory tests and other source documents including records of prior therapy and pathology
- Signed patient consent form
- HIPAA authorization form
- Assignation of a patient study number and randomization

• Register the patient on the study as per Winship Cancer Institute (WCI) standard operating procedures for participant registration. All consenting patients will be assigned an ID number consisting of the Winship study number (WINSHIP3112) followed by Arm on study (A for radiation arm and B for no radiation arm) the patients' first and last initials and the serial number at enrolment e.g. John Doe, the first enrolled patient on study, randomized to the no radiation arm will have the number WINSHIP3112AJD01.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab and tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the investigator as a solution for infusion after dilution.

5.1.1 Formulation/packaging/storage

Durvalumab

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.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution for infusion after dilution. The solution contains 20 mg/mL of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA); it has a pH of 5.5. The nominal fill volume is 20 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab must be used within the individually assigned expiry date on the label.

5.2 Dose and treatment regimens

5.2.1 Treatment regimens

Durvalumab + tremelimumab combination therapy

Patients in the durvalumab + tremelimumab combination therapy group will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w starting on

Week 17 for up to 8 months (9 doses) (see Figure 2). Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

5.2.2 Duration of treatment and criteria for retreatment

For patients receiving durvalumab + tremelimumab, retreatment is allowed (once only) for patients meeting the retreatment criteria below. The same treatment guidelines followed during the initial 12-month treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Patients receiving the combination of durvalumab and tremelimumab may undergo retreatment in 2 clinical scenarios, described below:

1. Patients who achieve and maintain disease control (i.e., CR, PR, or SD) through to the end of the 12-month treatment period may restart treatment with the combination upon evidence of PD, with or without confirmation according to RECIST 1.1, during follow-up.

2. Patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

3. For the durvalumab + tremelimumab treatment group, before restarting their assigned treatment, the Investigator should ensure that the patient:

    a. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient

    b. Still fulfils the eligibility criteria for this study, including re-consenting to restart durvalumab and tremelimumab

    c. Has not have received an intervening systemic anticancer therapy after their assigned treatment discontinuation.

d. Has had a baseline tumor assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial 12 months of treatment (relative to the date of randomization) until study treatment is stopped (maximum of 12 months of further treatment).

During the retreatment period, patients receiving durvalumab + tremelimumab may resume durvalumab dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for 4 doses each. Patients will then continue with durvalumab monotherapy at 1500 mg q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy (a total of 9 additional doses).

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. A patient with a confirmed progression receiving durvalumab + tremelimumab cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy (q4w dosing) and progression occurs in a target lesion that has previously shown a confirmed response. Patients will be required to provide written consent prior to restarting treatment or continuation of treatment in the presence of radiologic progression of disease,.

Patients who AstraZeneca and/or the Sponsor-Investigator determine may not continue treatment will enter follow-up.

5.2.3 Study drug preparation of durvalumab and tremelimumab

Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

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, 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 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0 mL of durvalumab (i.e., 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 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 tremelimumab and number of vials needed for the subject to achieve the accurate dose.

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 in the table, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab 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 tremelimumab 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

It is recommended that the prepared final IV bag be stored in the dark at 2ºC-8°C (36°F-46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Doses of 75 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter. Remove 3.8 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8 mL of tremelimumab (i.e., 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/mL to 10 mg/mL (IV bag volumes 50 to 500 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 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 <30 kg, Calculate the dose volume for tremelimumab and number of vials needed for subject to achieve the accurate dose.

Tremelimumab 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 tremelimumab, 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 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.

Tremelimumab 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 in the table, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

5.2.4 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

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 and re-initiated at 50% of the initial rate until completion of the infusion. For patients 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.

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 patients to an intensive care unit if necessary

5.2.5 Accountability and dispensation

The study drug provided for this study will be used only as directed in the study protocol. The IDS personnel will account for all study drugs. Drug accountability should be performed until

the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.

5.2.6 Disposition of unused investigational study drug

All unused study drugs will be destroyed on site according to standard practice employed by the IDS for appropriate destruction of study drugs. The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

5.3 Radiation Treatment

Patients in Arm II will receive palliative radiation (up to 30 Gy given as 5 fractions of 6 Gy administered daily for 1 week or 27 Gy given as 3 fractions of 9 Gy administered every other day for 1 week). Additional fractionation will be allowed based on site of lesion provided total radiation dose is completed within 1 week. The lesion selected for radiation will be safe for focal irradiation and medically appropriate for palliative doses of radiation. The target dose for a patient should conform to the normal tissue requirements in accord with standard radiation oncology practice.

6. TREATMENT PLAN

6.1 Subject enrollment and randomization

Eligible patients who have satisfied all the required inclusion and exclusion criteria will be randomized to Arm I or Arm II of the study. Patients in Arm I will receive systemic antibody therapy without preceding treatment with XRT while patients in Arm II will first receive priming radiation to a known site of disease involvement separate from the designated target lesions to be used for response assessment.

Radiation therapy will be delivered using standard XRT technique as deemed appropriate for the patient status and location of tumor. Treatment will be delivered within a week of randomization.

6.1.1 Procedures for randomization

Block randomization method will be used to assign patients randomly to the two groups. The block size of randomization is 2 to guarantee that each group will have equal number of 10 patients.

6.2 Blinding and procedures for unblinding the study

Not applicable

6.3 Dosage and Administration

Durvalumab (1500 mg durvalumab via IV infusion) + tremelimumab (75 mg tremelimumab via IV infusion) combination therapy will be administered to patients in Arm I and Arm II once every 4 weeks for up to 4 doses/cycles. Each 4-week interval is considered a cycle. Patients in Arm I will only receive the combination of Durvalumab and Tremelimumab while those randomized to Arm II will receive radiation treatment prior to starting treatment with Durvalumab/Tremelimumab. Following completion of 4 cycles of combination therapy, patients in both arms will continue 1500 mg durvalumab q4w starting on Week 16 for up to 8 months (9 doses) for a total of 1 year. Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Refer to Section 5.1.2, 5.1.3, and 5.2.4 for the administration and monitoring of administration of durvalumab and tremelimumab. Refer to Section 5.3 for radiation treatment administration for patients in Arm II.

6.4 Dose Escalation Decision Rules

Not applicable

6.5 Definition of DLT

Not applicable

6.6 Dose Modification and Toxicity Management

- 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 patients to an intensive care unit if necessary.

6.6.1 Durvalumab and tremelimumab

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 or tremelimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab and tremelimumab (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 or tremelimumab should be permanently discontinued.

Following the first dose of durvalumab or tremelimumab, subsequent administration of durvalumab or tremelimumab can be modified based on toxicities observed (see Table 1, 2, and 3 below).

Based on the mechanism of action of durvalumab or tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. 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 enterocolitis, dermatitis, hepatitis, and endocrinopathy 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, respectively.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 10.1.3. All toxicities will be graded according to NCI CTCAE v4.0.

Table 1- Immune-Mediated Reactions

	Dose Modifications	**Toxicity Management**
Immune-related Adverse Events (Overall Management For toxicities not noted below)	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.	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 1-2mg/kg/day PO 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 situation should be based upon a benefit/risk analysis for that patient
	Grade 1 No dose modification Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study treatment can be resumed once event stabilizes to Grade ≤1 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 judgment, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	

	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
	Grade 4	Permanently discontinue study drug/study regimen	
	Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen		

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Pneumonitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	General Guidance	– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to	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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		≤ Grade 1, then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	– If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/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 ≥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)[a] – 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)[a]

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	General Guidance	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) – Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	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 drug/study regimen can be resumed after completion of steroid taper	For Grade 2 diarrhea: – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[1]). **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])[a]
	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][a])

	Grade of the Event (NCI CTCAE version 4.03)	**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 Grade 1 (AST or ALT > to 3 times and/or TB > ULN to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications) 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 completion of steroid taper	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 PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone PO 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)[2] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation][a])

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	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 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 (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause.[b]	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][a])

	Grade of the Event (NCI CTCAE version 4.03)	**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	General Guidance	– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: - Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/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][a]). – 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 PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/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][a]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCICTCAE	General Guidance	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	version 4.03 for definition of severity/grade depending on type of skin rash)		
	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 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 PO or IV equivalent – Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥28 days and consider

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 4	Permanently discontinue study drug/study regimen	prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Discuss with Study Physician
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)	General Guidance	– 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.) – 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 of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	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 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.	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 treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

	Grade of the Event (NCI CTCAE version 4.03)	**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 Study drug/study regimen can be once event stabilizes 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])[a] – 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	General Guidance	– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	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 improves 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. IVIG)
	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.	For Grade 3 or 4: – Discuss with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) – Once stable, gradually taper steroids over ≥28 days
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-		General Guidance	– The prompt diagnosis of immune-mediated peripheral neuromotor

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis			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 (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 IVIG and followed by plasmapheresis if not responsive to IVIG
	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	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

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		30 days or if there are signs of respiratory insufficiency or autonomic instability	medications (e.g., gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study drug/study regimen if Grade 3 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 IVIG.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 4	Permanently discontinue study drug/study regimen	○ 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 IVIG and followed by plasmapheresis if not responsive to IVIG

Table 2- Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	– 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

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

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modification	Toxicity Management
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with 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.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation NCI NCI CTCAE version 4.03

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Females of childbearing potential who are sexually active with a non-sterilized male partner must use 2 methods of effective contraception (Table 2) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period; 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 post-menopausal (defined 12 months with no menses without an alternative medical cause).

Non-sterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 2) from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy, whichever is the longer time period.

Restrictions relating to concomitant medications are described in Section 7.2.

Table 4. Effective methods of contraception (2 methods must be used)

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

[a] This is also considered to be a hormonal method.

Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab or tremelimumab or until after 4-5X the half-life of durvalumab or tremelimumab or until the time specified in the prescribing information of durvalumab or tremelimumab, whichever occurs longest.

7.2 Concomitant treatment(s)

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.6 for guidance on management of IP-related toxicities.

7.2.1 Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 7.2.2.

All supportive measures consistent with optimal patient care will be given throughout the study. Supportive care (including IVF hydration) is not considered non-protocol therapy. Suggested supportive care medications may be substituted at the discretion of the investigator based on drug availability.

Enteral feeding and hyperalimentation may be used, but details must be clearly outlined on treatment forms.

The use of bisphosphonates or denosumab is allowed for patients with bone metastasis or hypercalcemia.

7.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy <<other than the protocol specified therapies>>

2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment, <<other than any stated comparator or combination regimens. Concurrent use of hormones for

noncancer-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 and tremelimumab dosing (i.e., 30 days prior to the first dose, during treatment with durvalumab and tremelimumab for 30 days post discontinuation of durvalumab and tremelimumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Table 5. Prohibited and Rescue Medications

Prohibited medication/class of drug:	**Usage:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment through 90 days after the last dose of IP.
Any concurrent chemotherapy, local therapy (except palliative radiotherapy for non-target lesions, e.g., radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment (including SoC). (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor α blockers	Should not be given whilst the patient is on IP treatment (including SoC). (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.

Prohibited medication/class of drug:	Usage:
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC) during the study

Rescue/supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., 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

8. STUDY PROCEDURES

8.1 Schedule of 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.

8.1.1 Screening Phase

Screening procedures will be performed up to 14 days prior to randomization and initiation of radiation therapy as applicable, except for baseline imaging (up to 28 days allowed) 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 screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Randomization
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart]
- Tumor biopsy
- Review of prior/concomitant medications
- Imaging by CT/MRI, if applicable to study
- Clinical laboratory tests for:
    - Hematology (see Table 6)
    - Clinical chemistry (see Table 7)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum or urine pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies
    - Urinalysis (see Table 8)
    - Baseline PD blood sample for cytokine and lymphocyte estimation (if feasible collect baseline samples before and after XRT in patients randomized to Arm II)
    -

8.1.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs, weight
- 12-lead ECG (in triplicate [≥1 minute apart]) on C3D1
- Review of prior/concomitant medications
- Repeat tumor biopsy prior to C3D1 treatment
- Clinical laboratory tests for:

- Hematology (see Table 6)
- Clinical chemistry (see Table 7)
- TSH
- Serum pregnancy test (for women of childbearing potential only)
- Hepatitis serologies (if clinically indicated)
- Urinalysis (see Table 8)
- PD blood sample for cytokine and lymphocyte estimation (C1D15, C2D1, C3D1 and at progression)

Arm I:

- Durvalumab, 1500 mg Q4W (equivalent to 20 mg/kg Q4W) for 12 months in patients ≥>> 30 kg
- Tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W) for up to 4 doses/cycles in patients ≥>>30 kg

Weight-based dosing should be utilized for patients <30 kg durvalumab 20 mg/kg Q4 and tremelimumab 1 mg/kg Q4. Patient may continue for an additional year of therapy if continuing clinical benefit and no safety concerns.

Arm II:

- Radiation to an isolated lesion (up to 30 Gy) by SBRT or hypofractionated conventional radiation delivery not to exceed 1 week
- Durvalumab, 1500 mg Q4W (equivalent to 20 mg/kg Q4W) for 12 months in patients ≥>> 30 kg
- Tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W) for up to 4 doses/cycles in patients ≥>>30 kg.

Weight-based dosing should be utilized for patients <30 kg durvalumab 20 mg/kg Q4 and tremelimumab 1 mg/kg Q4. Patient may continue for an additional year of therapy if continuing clinical benefit and no safety concerns.

Schedule of infusion of Durvalumab and Tremelimumab

Week	1 -4	5-8	9-12	13-16	17 -52
Cycle	1	2	3	4	5 -18

Durvalumab*	Q4W	Q4W	Q4W	Q4W	Q4W
Tremelimumab	Q4W	Q4W	Q4W	Q4W	NA

* 1500mg concurrent with tremelimumab in cycles 1to 4; 1500mg as single agent from cycle 5 onward

8.1.3 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 or tremelimumab 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 and tremelimumab treatment and achieved disease control, or have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progressive disease are provided in APPENDIX 1.

Assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in APPENDIX 2.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

8.2 Description of study procedures

8.2.1 Medical history and physical examination, electrocardiogram, 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.

8.2.2 Physical examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the

respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10

8.2.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At Screening, a single ECG will be obtained on which QTcF must be <470 ms.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 10.0.

8.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules.

On infusion days, patients receiving durvalumab + tremelimumab treatment will be monitored during and after infusion of IP as presented in the bulleted list below.

- Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving durvalumab + tremelimumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).

- Approximately 30 minutes during the infusion (**halfway** through infusion).

- At the end of the infusion (approximately 60 minutes ±5 minutes).

- A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or

after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Body weight is also recorded along with vital signs.

Situations in which vital signs results should be reported as AEs are described in Section 10.3. 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.

8.2.5 Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

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

Table 6. 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	

Table 7. Clinical chemistry (serum or plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
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 ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
[b] At baseline and as clinically indicated

Table 8. 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 and use the high power field for red blood cells

8.2.6 Patient reported outcomes (PRO)

Impact of treatment on patients' quality of life will be assessed by using PRO tools administered at baseline and with each restaging scans.

8.2.6.1 Name of PRO method or questionnaire

FACT-L questionnaire

8.3 Biological sampling procedures

PD marker including serum cytokines, chemokines along with peripheral lymphocyte repertoire and tumor infiltrating lymphocytes repertoire will be assessed at baseline, end of cycle 2 and at the time of progression if patient is deemed clinically stable and provide informed consent.

8.3.1 Pharmacokinetic sampling and evaluation methods

Not applicable

8.3.2 Immunogenicity sampling and evaluation methods

Not applicable

8.3.3 Biomarker/Pharmacodynamic sampling and evaluation methods

Serum Chemokine/Cytokine - Collect 5mls of peripheral blood into red tiger topped tubes at the designated time points (baseline, end of radiation, C1D15, C2D1, C3D1 and at the time of progression). Process blood sample by centrifugation at 1500g and collect the resultant plasma and serum as 1ml aliquots to be stored at -80°F until ready for analysis. Samples will be analyzed using the human 63-plex LUMINEX assay (BDNF, IL-21, SDF-1, bNGF, IL-22, sFas ligand, CD40L, IL-23, sICAM-1, EGF, IL-27, sVCAM-1, eotaxin, IL-31, TGF-alpha, ENA-78, IL-4, TGF-beta, FGF-2, IL-5, TNF-alpha, G-CSF IL-6 TNF-beta, GM-CSF, IL-7, TRAIL, GRO-alpha, IL-8, VEGF-A, HGF, IL-9, VEGF-D, IFN-alpha, IP-10, IFN-beta, leptin, IFN-gamma, LIF , IL-1-alpha, M-CSF, IL-10, MCP-1, IL-12p40 MCP-3, IL-12p70, MIG, IL-13, MIP-1-alpha, L-15, MIP-1-beta, IL-17A, PAI-1, L-17F, PDGF-BB, IL-18, PIGF-1, IL-1RA, RANTES, IL-1-beta, resistin, IL-2 and SCF).

Flow cytometry/FACS – Collect three tubes (5mls each) of whole blood samples into CPT tiger blue topped tubes for FACS to estimate peripheral circulating lymphocyte repertoire.

Peripheral blood samples will be collected into cell preparation tubes (BD Biosciences) and employed for PBMC isolation. PBMC will be immediately stained or frozen for later analysis. Single cell suspension will be isolated from biopsy samples harvested in cold L-15 Leibovitz media (HyClone). Tumors will be minced into small pieces and digested for 1h at 37°C with shaking by enzymatic cocktail of Collagenase I (125mg/1L), DNase I (50mg/1L), Collagenase IV (125mg/1L), Collagenase II (125mg/1L) and Elastase (50mg/1L) (Worthington). Single cell suspensions will be collected after RBC ACK lysis and cells will be stained for immediate analysis. Blood samples for flow cytometry should be submitted to the lab of Edmund K. Waller, MD, PhD

Winship Building B
5th Floor
Attn: Ernestine Mahar
Research Lab Manager
Emory University
Tel: (404)727-3086
Email: ernestine.a.mahar@emory.edu

Cell Free DNA (cfDNA) – Collect 30 mls of peripheral blood into Cell-Free DNA™ BCT (BCT) (Streck Inc., Omaha, NE) or purple topped EDTA tubes for plasma sample separation. Plasma samples for cfDNA should be dropped off in the lab of Taofeek Owonikoko, MD, PhD:

Winship Building C
3rd Floor Lab, Bench #20
Attention Guojing Zhang, MS
Tel: 404-778-1884
Email: guojing.zhang@emory.edu

Samples will be processed as detailed in Appendix 7

Summary of schedule of sample collection for pharmacodynamic analysis						
Biomarker assay and sample	Baseline	End of C1 D15	C2D1	C3D1	Progression	

type		XRT				
Tumor biopsy	X				X	X*
FACS: Collect three tubes (5mls each) of whole blood into CPT tiger blue topped tubes	X	X	X	X	X	X
Cytokine/Chemokine Collect one red tiger topped tube	X	X	X	X	X	X
cfDNA: collect 30mls of whole blood into Streck tubes or purple topped EDTA tubes	X	X	X	X	X	X
TILS by IHC or FACS: Place 3 biopsy cores for TILS in HyClone™ media and 1-2 cores for IHC in 10% buffered formalin.	X				X	X*
*: optional biopsy						

Tumor Biopsy – collect minimum of three to four cores using image guided biopsy (18-21Gauge needle) at baseline and at the time of 1st restaging scan (end of cycle 2 prior to C3D1 treatment) for all patients. Samples for TILS separation should be collected in cold L-15 Leibovitz media (HyClone™) while samples for IHC should be collected in 10% buffered formalin.

In appropriate and consenting patients, repeat biopsy at the time of disease progression. Employ 2 core aliquots for TILS assessment by FACS and 1-2 cores for IHC (PDL-1 expression and TILS). Please

FACS: PBMC and single cell suspension will be stained with anti-CD8 (RPA-T8), -CD4 (RPA-T4), -CD3 (UCHT1), -CD45RA (2H4LDH11LDB9), -CCR7 (150503), -PD-1

(EH12.2H7), -HLA-DR (l243), -CD38 (HIT2), -ICOS (ISA-3) -Bcl-2 (Bcl-2/100), -Ki67(B56), -CTLA-4 (BNI3), -Granzyme B (GB11), Foxp3 (236A/E7).

Panel	Markers	Remarks
T-Reg Activation Panel ICS*	CD3, CD4, CD8, ICOS, CD25, FoxP3*, CD69, CD38, CTLA4	
TIM3/PD-1 Panel	CD3, CD4, CD8, CD45RA, TIM3, PD-1, Lag3, Ki-67	
Homing Panel	CD3, CD4, CD8, Bcl-2, Granzyme B, CCR7	
ICS* Panel +/- PMA + Ionomycin	CD3, CD4, CD8, IFN gamma, IL-2, TNF, IL-4, Ki-67	
Dendritic Cell Panel	Lin-1, HLA-DR, CD123, CD11c, CD14, PD-L1, CD80, CD86, ICOS-L	

PD-L1 Testing

To ensure comparability of data across all studies of durvalumab and/or tremelimumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducible data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma,

cholangiocarcinoma, small cell lung, melanoma and cervical HPV+ cancers), the Ventana SP263 assay has only limited clinical performance data.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.

- In AstraZeneca studies, the preferred sample for PD-L1 testing was less than or equal to 3 months old. In cases where a sample a less than 3 months old was not available, patients were asked to undergo a new biopsy if considered clinically appropriate by their treating physician.

- 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 it is not older than 3 years of age. 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 (please submit to Winship Pathology Core Lab; 5th Floor Winship Building C). Samples from fine needle aspirate (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 testing

The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (ecode or unique identifier)
- Specimen identifier (written on the specimen)
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival orfresh tumor

- Tumor type
- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the Bio-Bank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.

- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and

embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.

- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended

- Below is the suggested routine overnight processing schedule:

Storage of tumor blocks for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 testing.

- Each sample should be reviewed for:

    - Adequate fixation
    - Good preservation of morphology
    - Presence of tumor tissue
    - Histopathology consistent with indication
    - Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

If indicated, shipping samples to a PD-L1 testing laboratory

- When submitting sample to for PD-L1 testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks should be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 micron thick) to be used for PD-L1 testing.

  Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for PD-L1 testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:

  - A minimum of 5-10 x 4 micron (μm) thick, unstained sections should be provided for PD-L1 testing
  - A new disposable microtome blade must be used for each block to prevent contamination between Slides are stable under these conditions for 6 months.
  - patient samples
  - Apply one section per slide to positively-charged Superfrost glass slides
  - The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status

8.3.4 Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 9 Volume of blood to be drawn from each subject (per cycle or for defined time points)

Assessment	Sample volume (mL)	No. of /Timepoints	Total volume (mL)
Biomarker			
FACS	15	6	90
Cytokine/Chemokine	5	6	30
cfDNA	10	6	60
Total			180

8.3.5 Archival tumor samples and fresh tumor biopsies

8.3.5.1 Archival tumor samples

Archival samples will be collected from all patients where feasible. This sample may be substituted for baseline tumor biopsy in the event that the patient does not have easily biopsable tumor site.

8.3.5.2 Fresh tumor biopsies

Mandatory fresh tumor biopsies will be collected from all subjects at baseline and prior to the administration of cycle 3 therapy (exception as in section 8.3.5.1 above). Samples will be collected by image-guided core needle biopsy, minimum of three core needle biopsies required at each time point in addition to samples collected for pathologic confirmation. An optional biopsy at the time of progression will be collected when feasible. Samples will be stored in three separate aliquots in the Winship lung satellite tumor bank refrigerator. Two aliquots will be employed to elute TILs to be subjected to FACS analysis while the third aliquot will be employed for IHC to detect PD-L1 expression and spatial distribution of TILs. Additional samples may be used for future genomic and metabolomic research if available.

8.3.6 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator: Taofeek Owonikoko, MD, PhD

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

9.1 RECIST Criteria v. 1.1

Patient response to treatment and overall clinical efficacy will be assessed according to RECIST 1.1 criteria. This assessment will be used to determine ORR, DoR, DCR, and PFS. OS will also be evaluated.

Cross sectional imaging (CT or MRI) will be the methods of assessment of tumor burden at baseline to include at the minimum, chest imaging to include the upper abdomen and any other areas of known disease involvement based on the signs and symptoms of individual patients.

The baseline assessment should be performed no more than 28 days before the start of treatment and as close as possible to the start of treatment. Efficacy for all patients will be assessed by objective tumor assessments Q8 weeks for the first 6 months (counting from the date of the first MEDI4736 or tremelimumab infusion) and then Q12 weeks thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment or subsequent therapy).

If an unscheduled scan is performed in the absence of suspicion of progression within 2 weeks of a scheduled scan, the scan does not need to be repeated. The next scan should be obtained according to the original schedule of imaging.

Disease progression requires confirmatory scan to be obtained at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment will continue between the initial assessment of progression and confirmation for progression.

Only patients determined not to have any significant, unacceptable, or irreversible toxicity, or continue to receive benefit from therapy can continue therapy through progression during the initial 12 months of therapy or restart a second 12 months of retreatment upon suspicion of PD. The patient must still meet all of the inclusion criteria and none of the exclusion criteria including reconsenting to continue or restart treatment.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue to receive study drug. Patients with confirmed progression cannot continue therapy or obtain retreatment if the progression occurred during dosing and after confirmed response in the target lesions (i.e., the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions).

Progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of target lesions compared with the nadir at 2 consecutive visits with an absolute increase of 5 mm(1)

- And/or significant progression (worsening) of non-target lesions or new lesions at the confirmatory PD time point compared with the first time point where progression of non-target lesions or new lesions was identified

- And/or additional new unequivocal lesions at the confirmatory PD time point compared with the first time point at which new lesions were identified.(1)

The assessment of progression requires a ≥20% increase in the sum diameters of target lesions at the first progression time point relative to the nadir. The nadir is the smallest sum of diameters, and this may be at baseline or subsequent follow-up assessments. The confirmatory scan confirms the persistence of the ≥20% increase relative to the nadir. The minimum absolute increase in the sum of diameters of target lesions is at least 5 mm at both assessments. In the absence of clinically significant deterioration, treatment should continue until progression is confirmed. If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD, and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR or PR) and SD will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

Objective tumor response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed. If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve "unequivocal progression" on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Following confirmed progression, patients should continue to be followed up for survival every 2-3 months as

outlined in the study plan. An exception are patients with confirmed PD who continue to receive IP at the discretion of the Investigator; these patients can receive treatment for a maximum of 12 months and will have scans for RECIST 1.1 assessments every 8 weeks (Q8W) (relative to the date of the first infusion) for 6 months and then every 3 months until disease progression.

Patients who achieve and maintain disease control (i.e., CR, PR, or SD) through to the end of the initial 12-month treatment period may restart treatment with the durvalumab + tremelimumab combination upon evidence of PD, with or without confirmation, during follow-up. To be eligible to restart treatment, the patient must not have received an intervening systemic anticancer therapy post discontinuation of initial treatment. Patients who restart treatment must have a baseline tumor assessment within 28 days of restarting treatment; all further scans should occur Q8W (relative to the date of restarting treatment) for the next 6 months and then Q12W until study treatment is stopped (maximum of 12 months of further treatment).

Patients who are eligible for retreatment will receive durvalumab (1500 mg/kg) via IV infusion Q4W for 4 months (4 doses) and tremelimumab (75 mg) via IV infusion Q4W for 4 months (up to 4 doses in total). After completion of the initial 4 doses of repeat combination therapy, single agent durvalumab will continue at 1500mg Q 4 weeks to complete 12 months of therapy. The first durvalumab dose at 1500 mg will be 4 weeks after the final dose of the combination of tremelimumab and durvalumab. It is important to follow the assessment schedule as closely as possible.

Immune-related Response Criteria (irRC)

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

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

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

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

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

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

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

9.1.1 Efficacy variable

Progression free survival (PFS): Measured from C1D1 until objective disease progression or death.

Objective response rate (ORR): According to RECIST 1.1 criteria based on cross sectional imaging obtained Q8W (after every 2 cycles) for the first 6 months and Q12W thereafter.

Disease control rate (DCR): Sum total of the proportion of patients with best response of complete response (CR), partial response (PR) and stable disease (SD).

Duration of response (DoR): Measured as interval of time from the first documentation of objective response (PR or CR) and subsequent progression of disease.

Subjects who have disease control following completion of 12 months of treatment or subjects who are withdrawn from MEDI4736 treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix B).

Subjects who have disease control following completion of 12 months of treatment or subjects who are withdrawn from durvalumab + tremelimumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix 3).

10. ASSESSMENT OF SAFETY

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

10.1.1 Safety Parameters

10.1.1.1 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 (including ECG 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.

10.1.2 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.

10.1.3 Durvalumab + tremelimumab adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring 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 and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs 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 aetiology. 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 Sponsor-Investigator.

AESIs observed with durvalumab and tremelimumab 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)

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator Brochure. For durvalumab and tremelimumab, AESIs will comprise the following:

AEs of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of durvalumab and tremelimumab safety profile and require close monitoring and rapid communication by the Investigator to AstraZeneca. Durvalumab and tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of these IPs.

Durvalumab, an anti-PD-L1 antibody, binds with high affinity and specificity to PD-L1 and blocks its binding to PD-1 (CD279) and B7-1 (CD80) molecules, thus promoting anti-tumor immunity and tumor cell killing. Tremelimumab, a CTLA-4 antibody, blocks the inhibitory signal resulting from CTLA-4 binding to B7 ligands on antigen-presenting cells, thus maintaining T-cell homeostasis. Potential risks based on these mechanisms of action include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neuropathy or neurologic events, pancreatitis, and pneumonitis.

The class including anti-PD-L1 drugs and other immune checkpoint antibodies, such as anti-PD-1 or anti-CTLA-4, have a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organ of the body.

For durvalumab and tremelimumab, AESIs will comprise the following:

Pneumonitis

AEs of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Table 1.

Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time. For all infusion reactions, SAEs should be reported to AstraZeneca Patient safety as described in Section 10.3.

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 (IgE-mediated) and anaphylactoid reactions against the mAbs 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 the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in Table 1.

Hepatic function abnormalities (hepatotoxicity)

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 IP. Guidelines for management of patients with hepatic function abnormality are provided in Table 1.

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving tremelimumab are provided in Table 1.

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 Table 1.

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 Table 1.

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 Table 1.

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 Table 1.

10.1.4 Immune-related adverse events

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558

(anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Hodi et al 2010, Brahmer et al 2012,). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Table 1, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab. These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (e.g., infliximab or mycophenolate).
- If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the Study Physician.

10.2 Assessment of safety parameters

10.2.1 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 9.2.1. 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.

10.2.2 Assessment of relationship

Attribution will be based on temporal relationship and whether or not the AE is anticipated for the procedure or investigational agent.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded in the electronic data capture system (Oncore™) 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 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 or tremelimumab (yes or no) <<and/or radiation (yes/no)>>
- Action taken with regard to durvalumab + tremelimumab/comparator/combination agent
- 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.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab + tremelimumab).

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 + tremelimumab. 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.

10.3.2 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 that written informed consent is obtained through 90 days after the last dose of durvalumab + tremelimumab 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 MedWatch/AdEERs form, of any serious or 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 MedWatch/AdEERs 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.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** 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-14-10531)

***** 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:*** AEMailboxClinicalTrialTCS@astrazeneca.com

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.

10.3.2.1 Reporting of deaths

All deaths that occur during the study or within the protocol-defined 90-day post-last dose of durvalumab + tremelimumab 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 AstraZeneca as a SAE within **24 hours** (see Section 10.3.2 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 MEDI4736 safety follow-up period will be documented <<as events for survival analysis>>, but will not be reported as an SAE.

10.3.3 Other events requiring reporting

10.3.3.1 Overdose

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

Any overdose of a study subject with durvalumab + tremelimumab, 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 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). 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 10.3 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

The investigator will use clinical judgment to treat any overdose.

10.3.3.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 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.

10.3.3.3 Pregnancy

10.3.3.4 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, i.e., 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.

10.3.4 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

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.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

All patients meeting eligibility requirement will be randomly assigned to one of two treatment groups. Block randomization method will be used to assign patients randomly to the two groups. The block size of randomization is 2 to guarantee each group will have equal number of 10 patients. The SAS version 9.3 is employed to generate the randomization table for patient assignment.

11.1 Description of analysis sets

11.1.1 Safety analysis set

All patients who received at least one dose of the study drug will be included in the safety analysis population

11.1.2 Efficacy analysis set

All patients who completed at least 2 cycles of therapy and underwent restaging scan will be included in the efficacy analysis. Patients who discontinued treatment due to toxicity may be replaced for the efficacy endpoint if treatment was stopped prior to the first restaging scan.

11.1.3 Randomization

All patients meeting eligibility requirement will be randomly assigned to one of two treatment groups. Block randomization method will be used to assign patients randomly to the two groups. The block size of randomization is 2 to guarantee each group will have equal number of 10 patients. The SAS version 9.3 is employed to generate the randomization table for patient assignment.

11.2 Methods of statistical analyses

All data will be listed individually by subject. Continuous variables will be summarized using descriptive statistics: mean, standard deviation, median, interquartile range and minimum and maximum values. Categorical variables will be summarized using number of subjects and proportion expressed as percentage. Baseline value for any specified variable is the last valid measurement before the administration of the study drug. Unless otherwise indicated, statistical significance will be declared if the two-sided p value is ≤ 0.05. All statistical analyses will be performed using SAS® Version 9.3 or higher.

Two-sided paired t-test will be used to compare biomarkers expressions between pre and post treatment samples. ANOVA and Kruskal-Wallis tests will be used to compare the degree of biomarker changes between the treatment groups. The proportion of patients with objective response will be estimated with exact 95% confidence intervals. Changes in pharmacodynamic endpoints will be correlated with response using Fisher exact test.

Missing Data Handling

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. For example, if an adverse event onset day is missing but the adverse event onset year and month can not exclude this adverse event as a TEAE, the adverse event will be flagged as a TEAE.

11.2.1 Safety Analyses

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations. These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTC http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf.

The occurrence of adverse events graded according to NCI CTCAE v. 4.3 criteria will be summarized using descriptive statistics. As far as possible, each adverse event should be evaluated to determine:

1. The type and severity using CTCAE v. 4.0 criteria
2. Its relationship to the study drug(s) (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam

11.2.2 Efficacy Analyses

The PFS will be measured from initiation of systemic therapy to first documented disease progression by RECIST criteria

PFS based on irRC guidelines will also be assessed.

Primary response assessment will be based on RECIST 1.1 criteria. Immune-related response criteria will also be assessed.

Data on patient demographics, tumor characteristics, response rate and pharmacodynamic (PD) biomarkers will be summarized using descriptive statistics. OS and PFS time will be analyzed using Kaplan Meier method. The proportion of patients with objective response will be estimated with exact 95% confidence intervals.

Comparisons will be performed between all patients (pooled across both arms) and historical control (topotecan) in terms of PFS and ORR. In addition, Arm 1 vs Arm II will be compared in terms of PFS and ORR, and possibly OS etc. Exploratory comparison of each Arm vs historical control will also be conducted.

11.2.3 Exploratory Analyses

Two-sided paired t-test will be used to compare biomarker differences between timed samples e.g. pre and post treatment samples. Pharmacodynamic biomarkers will also be correlated with efficacy. ANOVA and Kruskal-Wallis tests will be used to compare the degree of biomarker changes between the treatment groups and between various components of the FACT-L QoL questionnaire. Changes in pharmacodynamic endpoints will be correlated with efficacy (PFS, ORR, irRR) using Fisher exact test.

11.2.4 Interim analyses

Not applicable

11.3 Determination of sample size

For sample size determination, efficacy comparison was based on historical data with topotecan. Assuming a median PFS of 3 months if the intervention is no better than the historical PFS associated with topotecan based on the PFS from two recent randomized phase III studies of topotecan (Evans et al., 2015; von Pawel et al., 2014), and a promising median PFS of 7 months if the investigational treatment is superior (based on the duration of response recorded in a phase II study of combined PD-1 and CTLA-4 blockade in relapsed SCLC), 10 patients treated in each arm of the study will provide 87% power to demonstrate the hypothesized efficacy improvement at a 1-sided 10% alpha level test.

Similarly, with the same sample size of 10 patients in each arm, we will have 64% power at a 1-sided alpha of 10% to demonstrate a promising response rate of 30% for the investigational therapy versus the historical response rate of 10% with topotecan in the same patient population. Assuming an observed response rate of 30% (3 out of 10 patients) the 95% exact confidence interval of the response rate will be [6.7%, 65.2%] and 90% exact confidence internal of the response rate will be [8.7%, 60.7%].

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

12.2 Ethics and regulatory review

The Emory University Institutional Review Board (IRB) will have oversight responsibility and must approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The protocol will be re-approved by the EC/IRB annually or at any other interval deemed appropriate by the IRB.

AstraZeneca will provide Regulatory Authorities, ECs/IRBs, and Principal Investigators with safety updates or reports according to local requirements. Each Principal Investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

12.3 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

12.4 Changes to the protocol and informed consent form

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by AstraZeneca and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the FDA and IRB. Examples of amendments requiring such approval are:

1. Increases in drug dose or duration of exposure of subjects,
2. Significant changes in the study design (e.g. addition or deletion of a control group),
3. Increases in the number of invasive procedures
4. Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Astra Zeneca must be notified and the IRB at the center must be informed immediately.

13. STUDY MANAGEMENT

Investigators must enter study data onto case report forms (CRFs) or other data collection system. The Investigator will permit study-related audits by Emory IRB, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Novartis representative so that the accuracy and completeness may be checked.

13.1 Training of study site personnel

The study PI (sponsor-investigator) will provide training as appropriate to the delegated responsibility to all staffs involved in the conduct of the study. Before the first patient is enrolled in the study, study staff and co-investigators will review and discuss the requirements of the clinical study protocol and related documents including getting trained in any study-specific procedures and electronic data capture systems to be utilized.

The Sponsor-Investigator will ensure that appropriate training relevant to the study is given to all of these staff and any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

13.2 Monitoring of the study

13.2.1 Source data and documents

In accord with section 1.51 of the ICH E6 document all information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

13.2.2 Data Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

13.2.3 Data Safety and Quality Assessment

Data safety and quality assurance plan for this study will follow the established Data Safety and Monitoring Plan for all investigator-initiated clinical trials at the Winship (please refer Winship DSMP version 01/16/2015). The Emory Winship monitoring team will have primary responsibility to coordinate, conduct and/or oversee all study auditing. The study will be

monitored at least annually in addition to the reporting requirement established by the IRB. If the Monitoring Committee determined that an external audit should be conducted, the committee shall be responsible for appointing the external auditors upon discussion with AstraZeneca and its representative. The scope and conduct of the audit will be established by the committee and support for the audit will be provided by the Winship Monitoring Office.

Data integrity and safety information will be assessed as specified below:

i. Continuous monitoring by the PI

ii. DSMC monitoring team as per Winship SOP

iii. At least annually (review records for 2 patients or 20% of participants per year) or more frequently as determined by the committee

iv. At study closure.

The following will be inspected as part of the data monitoring assessment

i. Review of data integrity

ii. Delegation log and protocol training for investigators and other study staff

iii. Eligibility of consented/enrolled patients

iv. Informed consent document and process

v. Verification of adherence to protocol

vi. Accuracy, completeness and timeliness of data

vii. Accuracy and completeness of all source documentation

viii. Response evaluation: verify that responses are identified according to the protocol definition of response for any response that is a major endpoint

ix. Toxicity evaluation: verify that treatment-emergent toxicities are captured and graded accurately as specified by the protocol

x. Appropriate reporting of all AEs and SAEs as required by GCP, the protocol, IRB, regulations, sponsor's SOPs and other regulatory requirements (refer section 10.3)

The monitor shall meet with the designated research team members assigned to the trial to:

a) provide an itemized review of the deficiencies and remove items from itemized review which are corrected during this meeting

b) review and document corrections/the coordinator should indicate any remaining deficiencies and provide corrective action plan for resolution

c) prepare summary report for PI and Monitoring Committee to include summary of systematic deficiencies, significant protocol deviations, summary of remaining deficiencies and coordinator corrective action plan, recommendations for data collection and protocol revision for clarity

d) meet with the overall PI to discuss the report and document the PI's responses prior to submitting final report to the Monitoring Committee.

The final Monitoring Committee review of monitoring or audit report and PI response and PI summary of protocol to date will be included in the annual renewal submission. Egregious data insufficiencies that may impact the scientific integrity of the trial are reported to the Winship Associate Director of Clinical Research.

13.3 Study timetable and end of study

Number of patients & centers: A total of twenty eligible patients will be enrolled in the two arms of the study. This is a single center study to be conducted at the Emory University Winship Cancer Institute, an NCI-designated cancer center.

Population: Patients whose disease relapsed SCLC after prior therapy with a platinum-containing regimen and not more than two prior lines of therapy.

Study duration/timelines:

Total accrual duration: 24 months

Study start (FPFV): 02/01/2016

Recruitment end (LPFV): 01/31/2018

End of Study (LPLV): 08/31/2018

Completion of study report (CSR) - 11/30/2018

Publication date -03/31/2019

14. DATA MANAGEMENT

Data will be collected using an institutional electronic data recording system, Oncore. Electronic case report forms and study calendar will be generated prior to study activation.

14.1 Disclosure and confidentiality

The investigator will keep all information provided by AstraZeneca in strict confidence and will request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by AstraZeneca (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided to the investigator may not be disclosed to others without direct written authorization from AstraZeneca, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

14.2 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval).

14.3 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1 Identity of investigational product(s)

Table 9. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	1500 mg, solution, IV	MedImmune
Tremelimumab	75 mg, solution, IV	MedImmune

16. LIST OF REFERENCES

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

Antonia et al 2014b
Antonia S, Ou SI, Khleif SN, Brahmer J, Blake-Haskins A, Robbins PB, et al. Clinical activity and safety of MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody in patients with NSCLC. Poster presented at the European Society for Medical Oncology (ESMO) Meeting; 2014 Sep 26-30; Madrid, Spain.

Antonia et al 2014a
Antonia S, Goldberg S, Balmanoukian A, Narwal R, Robbins P, D'Angelo G, et al. A Phase 1 open-label study to evaluate the safety and tolerability of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in combination with tremelimumab in patients with advanced non-small cell lung cancer (NSCLC). Poster presented at European Society of Medical Oncology (ESMO) Meeting; 2014 Sep 26-30; Madrid, Spain.

Antonia et al 2015
Antonia et al. Phase ib study of medi4736 in combination with treme in patients with advanced NSCLC. Chicago, Il ASCO May30-June4,ASCO 2015, poster #3014.

Berry et al 1991
Berry G, Kitchin RM, Mock PA. A comparison of 2 simple hazard ratio estimators based on the logrank test. Stat Med 1991;10(5):749-55.

Bograd et al 2011
Bograd AJ, Suzuki K, Vertes E, Colovos C, Morales EA, Sadelain M, et al. Immune responses and immunotherapeutic interventions in malignant pleural mesothelioma. Cancer Immunol Immunother. 2011;60:1509-27.

Bonomi 2010
Bonomi PD. Implications of key trials in advanced nonsmall cell lung cancer. Cancer 2010;116(5):1155-64.

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65.

Brahmer et al 2014
Brahmer JR, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA et al. Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis [ASCO abstract 8112]. J Clin Oncol 2014;32(15)(Suppl).

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

Burt et al 2011
Burt BM, Rodig SJ, Tilleman TR, Elbardissi AW, Bueno R, Sugarbaker DJ. Circulating and tumor-infiltrating myeloid cells predict survival in human pleural mesothelioma. Cancer. 2011;117(22):5234-44.

Ciuleanu et al 2009
Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomized, double-blind, phase 3 study. Lancet 2009;374(9699):1432-40.

Collett 2003
Collett D. Modelling survival data in medical research: 2nd ed. Chapman and Hall/CRC; 2003.

D'Addario et al 2010
D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(Suppl 5):116-9.

Drake et al 2013
Drake CG, McDermott DF, Sznol M, Choueiri TK, Kluger HM, Powderly JD et al. Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up [abstract 4514]. J Clin Oncol 2013;31(Suppl).

Dunn et al 2004
Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

Ellis et al 2008
Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials 2008;29(4):456-65.

Forde et al 2014
Forde PM, Kelly RJ, Brahmer JR. New strategies in lung cancer: translating immunotherapy into clinical practice. Clin Cancer Res 2014;20(5):1067-73.

Gail and Simon 1985
Gail M, Simon R. Tests for qualitative interactions between treatment effects and patient subsets. Biometrics 1985;41(2):361–72.

GLOBOCAN 2012
GLOBOCAN. Lung cancer, estimated incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer, World Health Organization; Lyon, 2012. Available at http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed on 16 April 2015.

Gong et al 2009
Gong AY, Zhou R, Hu G, Li X, Splinter PL, O'Hara SP, et al. MicroRNA-513 regulates B7-H1 translation and is involved in IFN-gamma-induced B7-H1 expression in cholangiocytes. J Immunol 2009;182(3):1325-33.

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

Herbst et al 2013
Herbst RS, Gordon MS, Fine GD, Sosman JA, Soria JC, Hamid O, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumours [abstract 3000]. J Clin Oncol 2013;31(Suppl 15).

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

Hodi et al 2010
Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanan JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma [published erratum appears in N Engl J Med 2010;363(13):1290]. N Engl J Med 2010;363(8):711-23.

Hodi et al 2010
Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanan JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma [published erratum appears in N Engl J Med 2010;363(13):1290]. N Engl J Med 2010;363(8):711-23.

Hodi et al 2014
Hodi FS, Sznol M, Kluger HM, McDermott DF, Carvajal RD, Lawrence DP et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial [ASCO abstract 9002]. J Clin Oncol 2014; 32(15)(Suppl).

Howlander et al 2014
Howlander N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER cancer statistics review, 1975-2011. Bethesda (MD): National Cancer Institute,. Available from: URL:http://seer.cancer.gov/csr/1975_2011/ based on November 2013 SEER data submission (posted to the SEER web site, April 2014).

IASLC Staging Manual in Thoracic Oncology
Goldstraw P, ed. Staging manual in thoracic oncology. 7th ed. IASLC 2010. (Available on request)

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumour cells in the escape from host immune system and tumour immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99(19):12293-7.

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumour cells in the escape from host immune system and tumour immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99(19):12293-7.

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

Kirkwood et al 2010
Kirkwood JM, Lorigan P, Hersey P, Hauschild A, Robert C, McDermott D, et al. Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. Clin Cancer Res 2010;16(3):1042-8.

Kitano et al 2014
Kitano S, Postow MA, Ziegler CG, Kuk D, Panageas KS, Cortez C, et al. Computational algorithm-driven evaluation of monocytic myeloid-derived suppressor cell frequency for prediction of clinical outcomes. Cancer Immunol Res 2014;2(8):812-21.

Klein et al 2007
Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med 2007;26(24):4505-19.

Korn et al 2008
Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008;26(4):527-34.

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

Kresowik and Griffith 2009
Kresowik TP, Griffith TS. Bacillus Calmette–Guerin immunotherapy for urothelial carcinoma of the bladder. Immunother. 2009;1(2):281-8.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70(3):659-63.

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

McDermott 2009
McDermott DF. Immunotherapy of metastatic renal cell carcinoma. Cancer. 2009;115(10 suppl):2298–305.

Meyer et al 2014
Meyer C, Cagnon L, Costa-Nunes Cm, Baumgaaertner P, Montandon N, Leyvraz L, et al. Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab. Cancer Immunol Immunother 2014;63(3):247-57.

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

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

Nakano et al 2001
Nakano O, Sato M, Naito Y, Suzuki K, Orikasa S, Aizawa M, et al. Proliferative activity of intratumoral $CD8^+$ T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. Cancer Res. 2001;61:5132-6.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ (2013) Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet 52:1017–1027

Ng et al 2006
Ng CM, Lum BL, Gimenez V, et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.

NCCN 2014
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 4.2014. www.nccn.org.

Nishino et al 2013
Nishino M, Biobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19(14):3936-43.

Okudaira et al 2009
Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an anti-tumour effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252-64.

Paz-Ares et al 2013
Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31(23):2895-902.

Peggs et al 2009
Peggs KS, Quezada SA, Allison JP. Cancer immunotherapy: co-stimulatory agonists and coinhibitory antagonists. Clin Exp Immunol 2009;157:9-19.

Pisters and LeChevalier 2005
Pisters KM, LeChevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol 2005;23(14):3270-8.

Reck et al 2014
Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii27-39.

Ribas et al 2013
Ribas A, Kefford R, Marshall MA, Punt CJA, Haanen JB, Marmol M, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013;31:616-22.

Sandler et al 2006
Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355(24):2524-50.

Scagliotti et al 2008
Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-

naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21)3543-51.

Schadendorf et al 2013
Schadendorf D, Hodi FS, Robert C et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma. Presented at: European Cancer Congress 2013 (ECCO-ESMO-ESTRO); September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract 24.

Schiller et al 2002
Schiller JH, Harringdon D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;10(346):92-8.

Schwarzenbach et al 2014
Schwarzenbach H, Nishida N, Calin GA, Pantel K. Clinical evidence of circulating cell-free microRNAs in cancer. Nat Rev Clin Oncol 2014;11(3):145-56.

Selke and Siegmund 1983
Selke T, Siegmund D. Sequential analysis of the proportional hazards model. Biometrika 1983;70:315-26.

Sun and Chen 2010
Sun X, Chen C. Comparison of Finkelstein's Method with the conventional approach for interval-censored data analysis. Stat Biopharm Res 2010;2(1):97-108.

Tarhini and Kirkwood 2008
Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 2008;8(10):1583-93.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443-54.

Topalian et al 2014
Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol, 2014 Apr 1; 32(10):1020-30.

Wang et al 2009
Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.

Wang et al 2013
Wang Z, Han J, Cui Y, Fan K, Zhou X. Circulating microRNA-21 as noninvasive predictive biomarker for response in cancer immunotherapy. Med Hypotheses 2013;81(1):41-3.

Wang et al 2014
Wang E, Kang D, et al. Population pharmacokinetic and pharmacodynamics analysis of tremelimumab in patients with metastatic melanoma. J Clin Pharmacol. 2014 Oct; 54(10):1108-16.

Weber et al 2012
Weber J, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30(21):2691-7.

Whitehead and Whitehead 1991
Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991;10(11):1665-77.

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

Yuan et al 2011
Yuan J, Adamow M, Ginsberg BA, Rasalan TS, Ritter E, Gallardo HF, et al. Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlated with clinical benefit in advanced melanoma patients treated with ipilimumab. Proc Natl Acad Sci USA 2011;108(40):16723-8.

Zhang et al 2008
Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Anti-tumour immunotherapy by blockade of the

Zhang et al 2012
Zhang S, Shi R, Li C, et al. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.

1. Evans TL, Cho BC, Udud K, Fischer JR, Shepherd FA, Martinez P, Ramlau R, Syrigos KN, Shen L, Chadjaa M, Wolf M (2015) Cabazitaxel Versus Topotecan in Patients with Small-Cell Lung Cancer with Progressive Disease During or After First-Line Platinum-Based Chemotherapy. J Thorac Oncol 10 (8):1221-1228. doi:10.1097/JTO.0000000000000588

2. von Pawel J, Jotte R, Spigel DR, O'Brien ME, Socinski MA, Mezger J, Steins M, Bosquee L, Bubis J, Nackaerts K, Trigo JM, Clingan P, Schutte W, Lorigan P, Reck M, Domine M, Shepherd FA, Li S, Renschler MF (2014) Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol 32 (35):4012-4019. doi:10.1200/JCO.2013.54.5392
3. Tang C, Wang X, Soh H, Seyedin S, Cortez MA, Krishnan S, Massarelli E, Hong D, Naing A, Diab A, Gomez D, Ye H, Heymach J, Komaki R, Allison JP, Sharma P, Welsh JW (2014) Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer immunology research 2 (9):831-838. doi:10.1158/2326-6066.CIR-14-0069
Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, and Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res. 2011. 17(13):4232-4244.

Antonia, S.J., Bendell, J.C., Taylor, M.H., Calvo, E., Jaeger, D., Braud, F.G.D., Ott, P.A., Pietanza, M.C., Horn, L., Le, D.T., et al. (2015). Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. J Clin Oncol 33, suppl; abstr 7503.
Behera, M., Ragin, C., Kim, S., Chen, Z., Steuer, C.E., Saba, N.F., Pillai, R.N., Belani, C.P., Ramalingam, S.S., Khuri, F.R., et al. (2014). Trends in small cell lung cancer (SCLC) survival: Predictors and impact of systemic therapy. J Clin Oncol 32, abstr 7599.
Ben J. Slotman, C.F.-F., Harm van Tinteren, John Praag, Joost Knegjens, Sherif El Sharouni, Matthew Hatton, Astrid Keijser, Suresh Senan (2014). Randomized trial on thoracic radiotherapy (TRT) in extensive-stage small cell lung cancer. J Clin Oncol 32:5s, abstr 7502.
Blanquicett, C., Saif, M.W., Buchsbaum, D.J., Eloubeidi, M., Vickers, S.M., Chhieng, D.C., Carpenter, M.D., Sellers, J.C., Russo, S., Diasio, R.B., et al. (2005). Antitumor efficacy of capecitabine and celecoxib in irradiated and lead-shielded, contralateral human BxPC-3 pancreatic cancer xenografts: clinical implications of abscopal effects. Clinical cancer research : an official journal of the American Association for Cancer Research 11, 8773-8781.

Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65.

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

Callahan MK and Wolchok JD. CTLA-4 and PD-1 blocking antibodies in cancer immunotherapy. J Leukoc Biol. 2013; 94(1):41-53.

Chow et al. INSERT REFERENCE

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Deng, L., Liang, H., Burnette, B., Beckett, M., Darga, T., Weichselbaum, R.R., and Fu, Y.X. (2014a). Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. The Journal of clinical investigation 124, 687-695.

Deng, L., Liang, H., Burnette, B., Weicheslbaum, R.R., and Fu, Y.X. (2014b). Radiation and anti-PD-L1 antibody combinatorial therapy induces T cell-mediated depletion of myeloid-derived suppressor cells and tumor regression. Oncoimmunology 3, e28499.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) Food and Drug Administration Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf. Accessed 10 December 2013.

Guy C. Jones, J.B.M., Bruce E. Johnson, Kevin Camphausen, Eli Glatstein, Charles B. Simone, II (2014). Phase II study of low-dose rate thoracic radiotherapy for treatment of intrathoracic relapsed or progressive small cell lung cancer. Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA Philadelphia (PA): AACR; 2014 Abstract nr {CT343}

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

Hamid et al, 2013; INSERT REFERENCE

Kaehler et al, 2010; INSERT REFERENCE

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

Kim et al, 2013; INSERT REFERENCE

Koyama, K., Kagamu, H., Miura, S., Hiura, T., Miyabayashi, T., Itoh, R., Kuriyama, H., Tanaka, H., Tanaka, J., Yoshizawa, H., et al. (2008). Reciprocal CD4+ T-cell balance of effector CD62Llow CD4+ and CD62LhighCD25+ CD4+ regulatory T cells in small cell lung cancer reflects disease stage. Clinical cancer research : an official journal of the American Association for Cancer Research 14, 6770-6779.

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

Lenz et al, 2007; INSERT REFERENCE

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

Maddison, P., Newsom-Davis, J., Mills, K.R., and Souhami, R.L. (1999). Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. Lancet 353, 117-118.

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

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH and Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul; 19(14):3936-3943.

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic adenocarcinoma. Clin Cancer Res. 2007 Apr 1;13(7):2151-7.

Ott, P.A., Fernandez, M.E.E., Hiret, S., Kim, D.-W., Moss, R.A., Winser, T., Yuan, S., Cheng, J.D., Piperdi, B., and Mehnert, J.M. (2015). Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028. J Clin Oncol 33.

Owonikoko, T.K., Behera, M., Chen, Z., Bhimani, C., Curran, W.J., Khuri, F.R., and Ramalingam, S.S. (2012). A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol 7, 866-872.

Owonikoko, T.K., Ragin, C.C., Belani, C.P., Oton, A.B., Gooding, W.E., Taioli, E., and Ramalingam, S.S. (2007). Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol 25, 5570-5577.

Park J, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood. 2010;116(8):1291-8.

Pillai, R.N., and Owonikoko, T.K. (2014). Small cell lung cancer: therapies and targets. Seminars in oncology 41, 133-142.

Reck, M., Bondarenko, I., Luft, A., Serwatowski, P., Barlesi, F., Chacko, R., Sebastian, M., Lu, H., Cuillerot, J.M., and Lynch, T.J. (2013). Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 24, 75-83.

Schiller, J.H., Adak, S., Cella, D., DeVore, R.F., 3rd, and Johnson, D.H. (2001). Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593--a phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 19, 2114-2122.

Schiller, J.H., Kim, K., Hutson, P., DeVore, R., Glick, J., Stewart, J., and Johnson, D. (1996). Phase II study of topotecan in patients with extensive-stage small-cell carcinoma of the lung: an Eastern Cooperative Oncology Group Trial. J Clin Oncol 14, 2345-2352.

Shaw, A.T., Kim, D.W., Nakagawa, K., Seto, T., Crino, L., Ahn, M.J., De Pas, T., Besse, B., Solomon, B.J., Blackhall, F., et al. (2013a). Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368, 2385-2394

Shaw, A.T., Mehra, R., Kim, D.-W., Felip, E., Chow, L.Q.M., Camidge, D.R., Tan, D.S.-W., Vansteenkiste, J.F., Sharma, S., De Pas, T., et al. (2013b). Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC. Journal of Clinical Oncology 31, abstract 8010.

Siegel, R., Ma, J., Zou, Z., and Jemal, A. (2014). Cancer statistics, 2014. CA Cancer J Clin 64, 9-29.

Sznol M and Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. 2013; 19(5):1021-1034.

Tang, C., Wang, X., Soh, H., Seyedin, S., Cortez, M.A., Krishnan, S., Massarelli, E., Hong, D., Naing, A., Diab, A., *et al.* (2014). Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer immunology research *2*, 831-838.

Tani, T., Tanaka, K., Idezuka, J., and Nishizawa, M. (2008). Regulatory T cells in paraneoplastic neurological syndromes. Journal of neuroimmunology 196, 166-169.

Tarhini et al, 2013; INSERT REFERENCE

Thompson RH, Gillett MD, Chevillem JC, Lohsem CM, Dong H, Webster WS, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005;104(10):2084-91.

Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 2006;66(7):3381-5.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012 Jun 28;366(26):2443-54.

US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events Version 4.03. http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. World J Surg. 2010;34(5):1059-65.

Weber et al, 2012; INSERT REFERENCE

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-20.

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008;8(6):467-77.

APPENDIX 1

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

Evaluation	Time Since Last Dose of MEDI4736							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
Urine hCG or 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							
Pharmacokinetic assessment, if applicable			X					
Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in subject circulation), if applicable			X		X			
sPD-L1 concentration (to assess target engagement), if applicable			X					

APPENDIX 1

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

Evaluation	Time Since Last Dose of MEDI4736							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Patient questionnaire (patient reported outcomes)[c] and health resource use, if applicable	X		X	For subjects who achieve disease control following 12 months/48 weeks of treatment, patient questionnaires and information relating to health resource use should be completed every 12 weeks relative to the date of randomisation 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 and information relating to health resource use should be completed relative to the date of randomisation as follows: every 8 weeks for the first 48 weeks, then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review.					
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 12 weeks relative to the date of **first infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to **Error! Reference source not found.** for timings of confirmatory scans. For subjects who **discontinue MEDI4736 due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the relative to the date of **first infusion** as follows: every 8 weeks for the first 48 weeks, then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Events Table for timings of confirmatory scans. Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review 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.

[c] For patient questionnaires different approaches based on indication and study design

APPENDIX 2

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

Evaluation	Time Since Last Dose of MEDI4736							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
<<World Health Organisation>> <<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)
Urine hCG or serum βhCG	X							
Hematology	X	X	X					
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[c]	X							
Pharmacokinetic assessment, if applicable			X					
Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in subject circulation), if applicable			X					
sPD-L1 concentration (to assess target engagement), if applicable			X					
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumor and self antigens in circulation), if applicable	X							

APPENDIX 2

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

Evaluation	Time Since Last Dose of MEDI4736							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
miRNA/mRNA (to examine immune cell gene expression profiles in circulation), if applicable	X							
PBMCs, if applicable	X							
Patient questionnaire (patient reported outcomes)[d] and health resource use, if applicable	X		X					
Tumour assessment (CT or MRI)	For subjects who **continue on MEDI4736 post-confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of **first infusion** per Schedule of Events table until MEDI4736 is stopped. For subjects who **discontinue MEDI4736 following confirmed progression**, **scans should be conducted according to local clinical practice** and submitted for central review 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.

[d] For patient questionnaires different approaches based on indication and study design

APPENDIX 3: Durvalumab DOSE CALCULATIONS

For durvalumab dosing done depending on subject weight:

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 are 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) / 10.0 (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 4: Durvalumab DOSE VOLUME CALCULATIONS

For durvalumab flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000 / 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).

3. 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) / 10.0 (mL/vial)

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

Dose (mL) = 1.5 g ×1000 / 50 (mg/mL) = 30.0 mL

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

Number of vials = 30.0 (mL) / 10.0 (mL/vial) = 3 vials

APPENDIX 5: Tremelimumab DOSE CALCULATIONS

For tremelimumab dosing done depending on subject weight:

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 / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are 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) / 20.0 (mL/vial)

Example:

1. Cohort dose: 1 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 30 mg = 1 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 30 mg / 20 (mg/mL) = 1.5 mL

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

Number of vials = 1.5 (mL) / 20.0 (mL/vial) = 1 vials

APPENDIX 6: Tremelimumab DOSE VOLUME CALCULATIONS

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

Dose (mL) = X mg / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration

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

3. 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) / 20 (mL/vial)

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

Dose (mL) = 75 mg / 20 (mg/mL) = 3.8 mL

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

Number of vials = 3.8 (mL) / 20 (mL/vial) = 1 vial

APPENDIX 7: cfDNA Lab Blood Processing Protocol (version 122314 from Diehn's Lab)

❖ **Materials** (check to make sure you have all of it before you start)

- Filtered P2000 pipette tips
- P-2000 pipette
- 2.0-mL Eppendorf tubes
- Patient's blood - usually 30 mL in 3 "purple top" tubes (EDTA) per time point. Blood should be kept on ice or in refrigerator after drawing and processed as soon as possible to minimize lysis of WBCs and release of cellular genomic DNA into plasma

❖ **Methods**

1. Spin samples in the clinical centrifuge using the settings: 3,500rpm, 10min, 4C
2. While you wait, label tubes
3. After spinning, carefully remove lavender top tubes from centrifuge. Do not disturb the separated plasma and cell-free whole blood
    i. Tip: It helps to put all the tubes into one holder and carefully carry the holder to the hood
4. Using a filtered tip and p-2000 pipet aliquot ~1.8 mL clear plasma (not all the way to the top since tops of tubes tend to pop open upon freezing if filled all the way) into a 2.0 mL Eppendorf tube. Repeat until you have aliquotted the plasma from all the purple-top tubes into 2.0 mL Eppendorf tubes. With the tubes that have only the buffy coat and RBC remaining, mix the buffy coat and cell-free whole blood using a pipette tip and aliquot ~1.8 mL into a 2.0 mL Eppendorf tube. Repeat so you have a second 2.0 mL Eppendorf tube containing the buffy coat and RBC mixed together.
5. Put Eppendorf tubes into -80C freezer.
6. Record **# of plasma tubes stored, date of blood draw, time of blood draw, and time of storage**.
7. Samples will be shipped to the lab of Max Diehn at Stanford University for cfDNA analysis using CAPP-Seq technology.