9881

Investigational Drug	Durvalumab (MEDI4736) and tremelimumab
Substance(s)	Palliative hypofractionated radiation therapy
Study Number	*ESR-16-1185*
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Durvalumab (MEDI4736), Tremelimumab and Palliative Hypofractionated Image Guided Radiation Therapy (HIGRT) in patients with recurrent/metastatic squamous cell carcinomas of the head and neck previously treated with immune checkpoint inhibitors

Sponsor: University of Washington

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PROTOCOL SYNOPSIS

Clinical Protocol ESR 16 11857

Study Title: Durvalumab (MEDI4736), Tremelimumab and Palliative Hypofractionated Image guided Radiation Therapy (HIGRT) in patients with recurrent/metastatic squamous cell carcinomas of the head and neck previously treated with immune checkpoint inhibitors
Protocol Number: 9881 (ESR 16 11857)
Clinical Phase: I/II
Study Duration: 48 months
Investigational Product(s) and Reference Therapy: Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration after dilution. Tremelimumab will be supplied in glass vials containing 400 mg or 25mg of liquid solution at a concentration of 20 mg/mL for intravenous (IV) administration after dilution.
Research Hypothesis: Durvalumab, tremelimumab and hypofractionated palliative radiation therapy in combination is safe and well tolerated in patients with recurrent metastatic squamous cell carcinomas of the head and neck.
Objectives: **Primary Objective:** Demonstrate that durvalumab, tremelimumab and hypofractionated palliative radiation therapy is safe and well tolerated in patients with recurrent metastatic squamous cell carcinomas of the head and neck. **Secondary Objective(s)**: 1. Evaluate the objective response rate 2. Determine overall and progression free survival

Exploratory Objective(s):

Collect tumor and blood for correlative studies

Study Design:

This is a single arm, open label, prospective study evaluating the safety and clinical efficacy of the combination of durvalumab, tremelimumab and hypofractionated palliative radiation therapy (using either hypofractionated image guided radiotherapy (HIGRT) or Stereotactic ablative Body Radiation Therapy (SBRT)) in patients who have previously received immunotherapy agents.

All patients enrolled will receive:

1. Durvalumab 1500 mg IV Q4W x 13 doses
2. Tremelimumab 75mg IV Q4W x 4 doses
3. Hypofractionated palliative radiation therapy using either (HIGRT) or (SBRT) to a total dose of 24Gy given in 3 fractions every other day over 1 week to lung, bone, lymph node, soft tissue metastases or mediastinal lesions. Radiotherapy is to be initiated 2 weeks after the first dose of durvalumab and tremelimumab.

Number of Centers: 1

Number of Subjects:

A maximum of 20 subjects will be enrolled.

Study Population:

The study aims to enroll patients with recurrent metastatic squamous cell carcinomas of the head and neck, who have received a prior immune checkpoint inhibitor, and who have a target lesion (either local/regional or distant metastatic site involving the lung and/or mediastinum and/or bone and/or soft tissue lesions and/or lymph nodes , that requires local control for palliation, as determined by a multidisciplinary team.

Inclusion Criteria:

1. Histologically proven recurrent/metastatic squamous cell carcinoma arising from a previous head and neck primary site, and located within the head and neck region, lung mediastinum bone, , soft tissue, lymph nodes, and who are not candidates for curative intent therapy.

2. Be ≥18 years old at the time of signing informed consent and have an actual body weight > 40kg.

3. Demonstrated disease progression during, or after discontinuation, of the most recent line of systemic therapy.

4. Have received any number lines of prior systemic therapy (including systemic therapy in the curative intent setting, and including a platinum containing regimen).

5. Have received an anti-PD1 or anti PDL1 monoclonal antibody.

6. Have a target lesion/s deemed suitable by the treating physicians for hypofractionated radiation therapy (HIGRT or SBRT) with the intent of palliation or prevention of symptoms. This lesion must be: a) 1-3 non overlapping sites in the head and neck region OR b) metastatic lesions outside the H&N region in the lung mediastinum, soft tissue metastases, lymph nodes or bone (a minimum of 1 and a maximum 5 lesions will be irradiated), provided there is no significant overlap between the lesions. Patients should have RECIST 1.1 criteria measurable disease in addition to the lesion/s treated with radiation. If the site/s of radiation were previously radiated to high dose RT (>50Gy), there should be >6 month time interval between the last dose of radiation and the start of radiation.

7. Have the ability to tolerate required radiotherapy procedures(eg: lie flat and hold position for treatment) as determined by the treating physician

8. Be willing and able to provide written informed consent for the trial and comply with the study visit requirements

9. Have measurable disease based on RECIST 1.1. (in addition to the lesion/s that will be treated with hypofractionated radiation therapy)

10. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.

11. Have a performance status of 0 or 1 on the ECOG Performance Scale.

12. Demonstrate adequate organ function as defined in below, based on screening labs should be performed within 10 days of treatment initiation.

- Hemoglobin $\geq$ 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 > 60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

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

Females:

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

13. Evidence of post-menopausal status OR negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, or hysterectomy).

    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

14. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

15. Female subjects of childbearing potential should be willing to use 1 method of highly effective birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 180 days after the last dose of study medication (Reference Section 7.1). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

16. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study therapy.

17. Patient is ≥ 5 years free of another primary malignancy, except: a) if the other malignancy is basal cell carcinoma or cervical carcinoma in situ or b) if the other primary malignancy is not considered clinically significant and is requiring no active intervention

Exclusion Criteria:

The subject ***must be excluded*** from participating in the trial if the subject:

1. Has a body weight ≤40kg at the time of enrollment

2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3. Has a target lesion/s for radiotherapy that is > 5 cm (> 50 cc) in greatest dimension

4. Has a target lesion/s in a region that previously received high dose RT (>50 Gy) demonstrating any of the following:
    a. carotid artery encasement (> 180 degrees)
    b. unprotected carotid artery (i.e. skin is directly over the carotid without intervening soft tissue, especially after prior neck dissection without a vascularized free flap) (a&b due to risk of carotid blow out)
    c. skin infiltration by tumor (due to risk of fistula)
    d. located in the larynx/hypopharynx primaries (due airway threat)
    e. treated with high dose radiation therapy (>50 Gy) within 6 months or less of trial enrollment

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

6. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:

    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)

    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication

7. Has received a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

8. Has received prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   -Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

   -Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

9. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

10. Has known brain metastases or spinal cord compression unless the patient is stable (asymptomatic; no evidence of new or emerging brain metastases; and stable and off steroids for at least 14 days prior to start of study treatment). Following radiotherapy and/or surgery of the brain metastases patients must wait 4 weeks following the intervention and before initiating study treatment with imaging to confirm stability.

11. Has an active autoimmune disease requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study.

12. Has evidence of current interstitial lung disease (ILD) or pneumonitis or a prior history of ILD or pneumonitis requiring oral or intravenous glucocorticoids.

13. Has an active infection requiring systemic therapy.

14. Requires therapeutic anticoagulation or has known active bleeding diathesis

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 180 days after the last dose of trial treatment.

18. Has received prior therapy with an anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

20. Has evidence of acute or chronic hepatitis B, or hepatitis C

21. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

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

23. Has a history of primary immunodeficiency or an allogeneic organ transplant

24. Has a history of hypersensitivity to durvalumab or tremelimumab excipient

25. Known history of previous clinical diagnosis of tuberculosis

26. Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, seizures

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

Durvalumab, 1500 mg Q4W (equivalent to 20 mg/kg Q4W) via IV infusion for up to 13 doses (fixed dose for patients > 30kg)

Tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W) via IV infusion for up to 4 doses (fixed dose for patients > 30kg)

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Patients enrolled in the study will be evaluated by the investigator/co-investigator prior to each dose of durvalumab and tremelimumab (more frequently if clinically indicated), and assessed for adverse events. All adverse events will be graded via CTCAE v. 4.

Efficacy Assessments:

RECIST criteria 1.1 will be used to evaluate treatment responses in all patients enrolled on the study. Patients will have baseline imaging obtained within 4 weeks of starting the investigational agents. Repeat imaging will be performed every 8 weeks (+/- 1 week).

Pharmacodynamic / Pharmacokinetic Assessments (if applicable):

None

Statistical Methods and Data Analysis:

The primary objective of this study is to evaluate the safety and tolerability of durvalumab and tremelimumab with hypofractionated radiation therapy in patients with recurrent head and neck cancer who have previously received immunotherapy. The total sample size for this evaluation is 20 patients evaluated in a dose de-escalation design. Initially, durvalumab dosing will be 1500 mg IV Q4weeks and tremelimumab dosing will be 75mg IV Q4W.

Both durvalumab and tremelimumab have well established toxicity profiles as a single agent and in combination. However, the combination of durvalumab tremelimumab and palliative radiation has not been previously studied, this study will include a formal safety analysis in the first 6 patients accrued. Enrollment will be halted until these first 6 patients complete the first two cycles of treatment (8 weeks), and are evaluable for acute toxicities (toxicities reported within the 1st 8 weeks after treatment initiation). Specifically, if 2 or more DLTs (Refer to Section 6.4) are observed, then, durvalumab dosing will be modified to 1500 mg IV Q6 weeks x 9 doses and tremelimumab 75mg IV Q6 weeks x 3 doses for the remaining 14 patients (fixed dosing for patients > 30kg). If 1 or fewer DLTs are observed, then an additional 14 patients will be enrolled and treated at the initial dose and schedule of durvalumab and tremelimumab. Patients in the run in phase who experience DLTs will undergo dose modifications described in Appendix 1.

Toxicities will be graded based on CTCAE v. 4 and summarized as the number and percentage of patients with each type of toxicity. Responses will be summarized as frequencies and percentages. The Kaplan Meier method will be used to estimate overall survival and progression free survival. Outcomes will be calculated from the date of study entry to the date of the corresponding event.

We will use multivariate statistics to test the hypotheses that pretreatment intratumoral immune cell phenotype and PD-L1 expression predict response to therapy, and that therapy alters systemic immunophenotype.

Sample Size Determination:

There are multiple ongoing studies in various tumor types exploring the activity of durvalumab and tremelimumab. In a published report of the combination in patients with advanced NSCLC treated on a phase Ib study, Grade 3-4 toxicity was observed in 17% of patients. Similarly, in single institution reports of SBRT with the monoclonal antibody, grade 3 or higher toxicity was reported in 6-16% of patients. With a 20 patient accrual goal, toxicity rates can be estimated to within 22% with 95% confidence. Any toxicity with at least 10% prevalence has at least an 87% chance of being observed. This design allows us to reasonably exclude a clinically significant increase in toxicity with the addition of radiation therapy to the durvalumab and tremelimumab combination as defined by the upper bound of the confidence interval.

The response rates to dual CTLA and PDL1 blockade and radiation therapy after prior immunotherapy are unknown. If objective responses are demonstrated, or encouraging progression free survival is observed in the 20 patients enrolled on the study, it would merit further investigation in a larger study powered to examine efficacy endpoints.

SCHEDULE OF STUDY ASSESSMENTS

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject	Screening	all assessments to be performed pre-infusion unless stated otherwise				
		cycle 1		cycle 2 - 4	cycle 5 -13	
		week 1	week 3	week 1	week 1	end of treatment
Day	**- 28 to - 1**	**Day 1 of the Week**				
Week	**-4 to -1**	**(±3 days)**			**(±7 days)**	
Written informed consent	X					
Demography and history of tobacco and alcohol use	X					
Previous treatments for head and neck cancer	X					
Tumor tissue sample (Section 8.3.2)	X					
Formal verification of eligibility criteria	X					
Medical and surgical history	X					

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject	Screening	all assessments to be performed pre-infusion unless stated otherwise					
		cycle 1		cycle 2 - 4	cycle 5 - 13		
		week 1	week 3	week 1	week 1	end of treatment	LTFM
Day	**- 28 to - 1**	**Day 1 of the Week**					
Week	**-4 to -1**	**(±3 days)**			**(±7 days)**		
Urine hCG or serum βhCG[b]	X						
Physical examination[c]	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	
Weight	X	X		X	X		
Electrocardiogram[d]	X						
Durvalumab administration[e]		X		X	X		
Tremelimumab administration[e]		X		X		X	
Adverse event/serious adverse event assessment	X	All Visits					
Radiation therapy evaluation and radiation planning/simulation	X						
Palliative Radiation therapy		XRT to begin 2 weeks after the first dose of Durvalumab and tremelimumab and to be completed in 2 weeks					
ECOG performance status	X	X	X	x	X	X	

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject	Screening	all assessments to be performed pre-infusion unless stated otherwise					
		cycle 1		cycle 2 - 4	cycle 5 - 13		
		week 1	week 3	week 1	week 1	end of treatment	LTFM
Day	**- 28 to - 1**	**Day 1 of the Week**					
Week	**-4 to -1**	**(±3 days)**			**(±7 days)**		
TSH with reflexive free T4 [f]		X		X [f]	X [f]		
Complete blood count[g]	X	X	X	X	X	X	
Serum chemistry[g]	X	X	X	X	X	X	
Urinalysis[h]	X		X				
Coagulation parameters[i]	X	as clinically indicated					
Correlative blood samples [j]	X			X[j]			
Tumor assessments[k]	X			X	X	X	

[a] A maximum of 20 patients will be included in the trial.

[b] Pre-menopausal female subjects of childbearing potential only

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

[d] ECG during screening. Thereafter as clinically indicated. Baseline and abnormal ECG at any time in triplicate.

e The administration of durvalumab and tremelimumab will be held if weight ≤30kg.

f Add free T4 if TSH is abnormal. Repeat at least every 12 weeks.

g 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 blood test must be available and reviewed before commencing an infusion.

h Urinalysis performed at Screening and then as clinically indicated.

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

j Correlative blood samples will be collected to prior to the first dose and prior to c2 and c4.

k Timing of CT scans for tumor assessments will be every 8 weeks (+/- 1 week).

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ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
3D CRT	3-dimensional conformal radiotherapy
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
CSR	Clinical study report

Abbreviation or special term	Explanation
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
HIGRT	Hypofractionated Image Guided Radiotherapy
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
IMRT	Intensity modulated radiotherapy
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
SBRT	Stereotactic ablative Body Radiotherapy
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_4	Thyroxine

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

1. INTRODUCTION

The immune checkpoint inhibitors have activity in patients with recurrent metastatic head and neck squamous cell carcinomas. However, current clinical data indicates that a minority of patients benefit from this approach, with objective response rates ranging from 13-27%, in various reported clinical trials using both anti-PD1 and anti-PDL1 antibodies as single agents. There is now increasing interest in studying mechanisms of immune escape in patients who do not respond to these immune checkpoint inhibitors.

The dual inhibition of PDL-1 and CTLA-4 is an approach that has garnered significant enthusiasm, due to robust preclinical data showing synergistic antitumor efficacy. This data is supported by prospectively collected clinical data, in immunotherapy naive melanoma patients, wherein improved objective response rates and progression free response rates were observed with the combination of nivolumab and ipilimumab compared to either agent alone. Multiple ongoing studies in other tumor types are examining the activity of this combination. In addition, responses with the anti-CTLA4 antibodies after non-response to prior PD-1 or PDL-1 monoclonal antibodies have been described in melanoma patients.

The role of radiation therapy in transforming the tumor microenvironment to increase the activity of immune checkpoint inhibition is an area of significant scientific interest. There is preclinical data supporting that the exposure to immune checkpoint inhibitors prior to therapeutic radiation is associated with increased antitumor activity. The clinical observation of the abscopal effect further supports the potential clinical utility of radiation therapy in inducing responses to immune check point inhibition.

We hypothesize that the combination of durvalumab, tremelimumab and palliative hypofractionated radiation among patients previously treated with immune checkpoint inhibitors is not only safe and feasible, but will result in the induction or restoration of responses to immune checkpoint inhibition and subsequent clinical benefit and improved survival in this refractory patient population.

1.1 Disease Background

Immune responses directed against tumors are one of the body's natural defences 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).

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).

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 (Peggs et al 2009). 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 10).

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, Okudaira et al 2009. Zhang et al 2008).

To date durvalumab has been given to more than 1800 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized Section 14.2.1 and in the durvalumab IB version 10.0 which details the complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

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 ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.

As of 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 7.0).

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 (**Error! Reference source not found.**). 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. To date tremelimumab has been given to more than 1000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section.1.4.2.2. Refer to the current tremelimumab Investigator's Brochure (v.7) for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

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 (Pardoll 2012) 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.

1.1.5 Radiation therapy

Uncontrolled loco regional disease is a major concern in head and neck cancer as it severely compromises a patient's quality of life with pain, ulceration, bleeding, foul odor, speech, swallowing, and breathing difficulties etc. Historically, radiation therapy has underpinned any and all attempts at providing durable disease control in the head and neck region.

In this protocol, palliative radiation therapy will be administered using either hypofractionated Image guided Radiotherapy (HIGRT) or Stereotactic ablative body radiotherapy (SBRT). These two techniques involve precise delivery of large tumoricidal/ablative doses of radiation treatments to a smal tumor over 1-5 fractions using image guidance and elaborate treatment planning process aimed at providing steep dose gradients especially near critical organs. Distinct nontraditional radiobiological mechanisms may be involved with the high dose fractions (>/= 6 Gy) used with HIGRT/SBRT, as compared with conventionally fractionated (1.8-2 Gy) radiotherapy that is commonly used in the curative setting. HIGRT/SBRT may produce biological effects mediated through enhanced immune stimulation and endothelial damage of the tumor micro environment. (Karam et al. Future Oncol. 2015). As a primary modality for medically unfit patients, SBRT has offered reasonable local control with acceptable toxicity. In the re-irradiation setting, SBRT is associated with higher rates of morbidity (10-50%) and even mortality (1-5%) in the face of promising local control.

There is now increasing data on the feasibility of hypofractionated radiation administered concurrent with immune checkpoint inhibition. Recent publication of the randomized phase 2 SABR-COMET study (Palma et al. Lancet 2019) (SBRT) in the oligometastatic setting significantly improves overall survival and progression free survival compared to palliative standard of care. This trial targeted all known metastatic lesions and was not in combination

with immunotherapy. However, it does indicate a role for hypofractionated ablative radiotherapy in the metastatic setting and demonstrates that it can be used safely to prolong survival. McBride, et al, presented preliminary data in abstract form (ASCO 2018 abstract #6009), randomizing 53 patients with recurrent/metastatic head and neck cancer to nivolumab alone, or nivolumab with SBRT. Although no survival advantage was noted in the nivolumab + SBRT arm was noted int this study, the benefit of dual PD1 and CTLA 4 inhibition with SBRT is unknown in this population, and it supported by compelling preclinical data (Twyman St. Victor, Nature 2015). Additionally, Lemons et al (ASCO-SITC 2018 Abstract #20) presented data on a phase I clinical trial of pembrolizumab and SBRT in 73 patients with various solid tumors. No radiation dose reductions were necessary, 13.2% of patients had an abscopal response.

1.2 Research hypothesis

Based on the prior experience with the combination of durvalumab and tremelimumab, we hypothesize that the combination of these two at the fixed dose of 1500 mg and 75 mg Q28 days respectively given with hypofractionated radiation therapy (either HIGRT or SBRT), would be a well-tolerated and feasible treatment for patients (> 30kg) with head and neck cancer previously treated with immunotherapy.

There is also no available data on the activity of the combination blockade of CTLA4 and PD1 in the setting of prior exposure to an anti-PD1 or PDL1 agent, therefore, hypothesis generating data on the objective response rates in this population will be collected and used to determine if further study of this combination is worth pursuing.

1.3 Rationale for conducting this study

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 (Pardoll 2012). 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 (Wolchock et al, 2013). Similar results have been observed in an ongoing study of durvalumab +

tremelimumab in NSCLC (), with further updated details presented in this clinical study protocol.

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 both 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. Altogether, 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 (**Error! Reference source not found.**).

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 (**Error! Reference source not found.**).

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, **Error! Reference source not found.**).

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.

1.3.3 Rationale for the combination of durvalumab, tremelimumab and hypofractionated radiation therapy (HIGRT or SBRT)

There are both preclinical and clinical data supporting the immunogenic potential of radiation therapy. Exposure to radiation therapy appears to result in priming the anti-tumor T cells within the tumor microenvironment to tumor antigens. There is also data supporting the increased efficacy of hypofractionated radiation in stimulation of the immune system against tumor antigens. This therapeutic approach is currently being actively tested in various tumor types including head and neck cancer.

1.4 Benefit/risk and ethical assessment

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 (**Error! Reference source not found.**). 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 (**Error! Reference source not found.**). 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 (eg, 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.

1.4.1.4 Radiation therapy

Squamous cell carcinomas are known to be sensitive to radiation therapy, and therefore it is a treatment modality that has well defined roles in the definitive setting. Radiation therapy is likewise a useful therapeutic modality in patients who require local therapy for palliation of symptoms. In addition to the potential benefit of local control and alleviation of tumor burden related symptoms, encouraging data is emerging that associates hypofractionated radiation potential with release of tumor related antigens, and possible synergy with immune checkpoint inhibition. Furthermore, The SABR-COMET study (Palma et al. Lancet 2019) indicates that stereotactic ablative radiotherapy (SBRT) in the oligometastatic setting significantly improves overall survival and progression free survival compared to palliative standard of care.

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 (**Error! Reference source not found.**), using the combination of the same class of drugs (eg, 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 (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

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 (5^{th}, median and 95^{th} 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 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.

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 will not be included in this study.

1.4.2.5 Hypofractionated radiation therapy (HIGRT or SBRT)

The potential benefit of combining HIGRT or SBRT with immune therapy is to synergize the local immune stimulatory properties of hypofractionated radiation therapy with the systemic immune stimulatory properties of a CTLA-4 (Tremelimumab) and an anti PDL-1 inhibitor (Durvalumab). In animal models, it is known that compared to multiple fractions of RT, fewer fractions of RT minimize the killing of the exquisitely sensitive T lymphocytes that folk to the immunogenic tumor microenvironment (Lee et al Blood 2009;114:589-95).

Radiation therapy is not without toxicity, and therefore to limit adverse radiation related events, the inclusion and exclusion criteria will include parameters for the HIGRT or SBRT treated lesions. Specifically, only 1-5 lesions will be treated, these should be non-overlapping

lesions, that are either previously not radiated, or if previously radiated to >50Gy, a 6 month time interval between the last dose of RT and HIGRTor SBRT will be required.

2. STUDY OBJECTIVES

2.1.1 Primary objective

The primary objective of this study is to demonstrate safety and tolerability of durvalumab and tremelimumab and palliative radiation therapy in patients with recurrent metastatic squamous cell carcinomas of the head and neck previously exposed to an anti PD-1 or PDL-1 monoclonal antibody

2.1.2 Secondary objective(s)

2.1.2.1 Measure objective response rates based on RECIST 1.1. criteria in patients receiving the durvalumab, tremelimumab and palliative RT combination

2.1.2.1 Determine overall and progression free survival in patients enrolled in the study

2.1.3 Exploratory objective(s)

2.1.3.1 Collect serum and archived (or fresh) tissue for correlative studies.

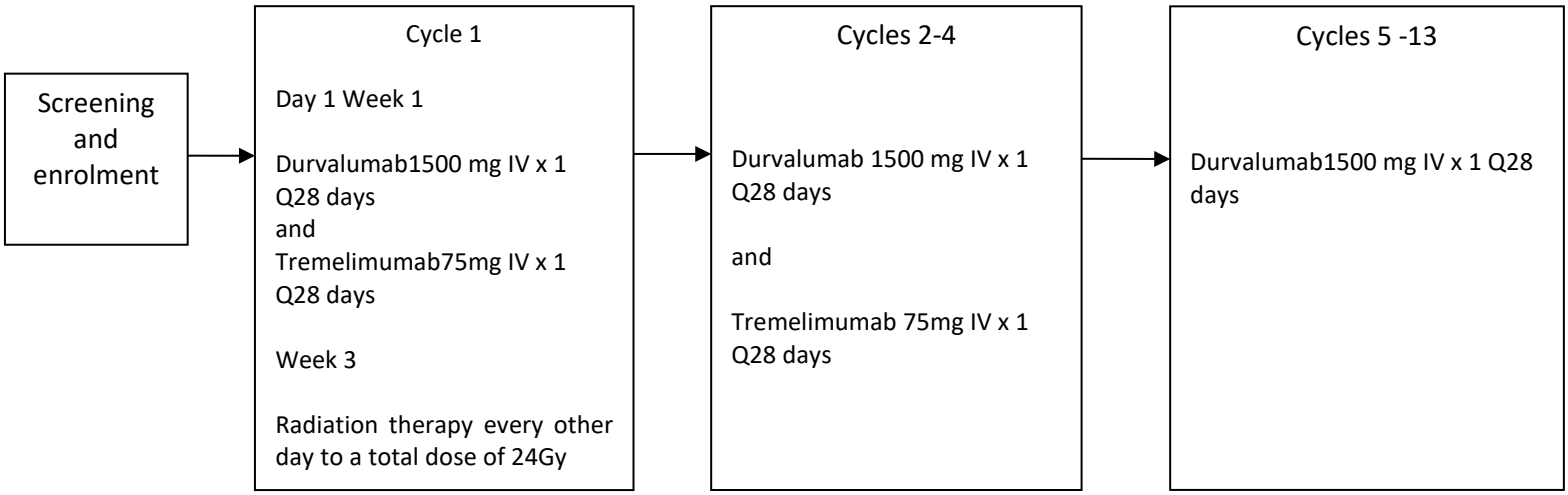
3. STUDY DESIGN

3.1 Overview of study design

This study will be carried out as a single institution, single arm phase I/II unblinded trial. A maximum of 20 patients will be enrolled. Each patient will be treated with durvalumab, tremelimumab and palliative hypofractionated radiation therapy using either HIGRT or SBRT. Durvalumab will be continued for 13

cycles, unless evidence of unacceptable toxicity, disease progression or withdrawal of patient consent were to occur.

3.2 Study Schema



The first 6 patients of this study will represent the initial run-in phase of the triplet combination of durvalumab, tremelimumab and HIGRTor SBRT. Fixed doses of Durvalumab and Tremelimumab will be administered on day 1 of therapy. Radiation will be initiated on Week 3 of the 28 day cycle. Radiation will be delivered to a total dose of 24 Gy, given in 3 fractions of 8Gy every other day. Durvalumab will be continued for a total of 13 cycles, and tremelimumab for a total of 4 cycles unless patient withdraws consent, has confirmed disease progression, and/or develops toxicity that results in treatment discontinuation.

Serum correlative studies will be collected at the following timepoints: at baseline, prior to cycle #2, and prior to cycle#4 of treatment. Archived formalin fixed paraffin embedded tissue will be collected from patients enrolled. If the patient does not have archived tissue available, a fresh biopsy will be obtained.

3.3 Study Oversight for Safety Evaluation

The primary endpoint of this study is safety and tolerability. Durvalumab and tremelimumab will be given at the recommended fixed dosing in patients > 30kg (see section 1.3.1), which has been shown to result in minimal toxicity, but encouraging efficacy in NSCLC patients. Since the concurrent administration of radiation therapy is previously unstudied in this cohort, the first 6 patients will represent a run-in phase, and enrollment will be halted until all patients complete

the first two cycles of treatment (8weeks) These 6 patients will be assessed for DLTs and will determine if a modified dosing schedule of durvalumab and tremelimumab will be applied in the expansion phase.

In keeping with the study primary endpoint, a stopping rule will be implemented in the unlikely event that the combination under study is deemed to have unacceptably high toxicities. Enrollment will be halted if more than 3 patients experience a Grade 4 or higher drug related toxicity (CTCAE v. 4) during the trial or up to 30 days after the last investigational drug infusion. The likelihood of observing 3 or more Grade 4+ drug-related DLTs is 80% if the true rate is 20% and the likelihood is 91% if the true rate is 25%. This rule has an 83% chance of stopping in the 1st 10 patients if the true rate is 40%. Section 10.2.2 provides some guidelines on the attribution of toxicity to the drug and radiation combination. The study will be reviewed by the University of Washington/Fred Hutchinson Cancer Research Center Data Safety and monitoring board.

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

1. Histologically proven recurrent/metastatic squamous cell carcinoma arising from a previous head and neck primary site, and located within the head and neck region, lung mediastinum, lymph nodes, soft tissue metastases or bone, and who are not candidates for curative intent therapy.

2. Be ≥18 years old at the time of signing informed consent and have an actual body weight > 40kg.

3. Demonstrated disease progression during, or after discontinuation, of the most recent line of systemic therapy.

4. Have received any number lines of prior systemic therapy (including systemic therapy in the curative intent setting, and including a platinum containing regimen).

5. Have received an anti-PD1 or anti PDL1 monoclonal antibody.

6. Have a target lesion/s deemed suitable by the treating physicians for hypofractionated radiation therapy (HIGRT or SBRT) with the intent of palliation or prevention of symptoms. This lesion must be: a) 1-3 non overlapping sites in the head and neck region OR b) metastatic lesions outside the H&N region in the lung mediastinum, soft tissue metastases, lymph nodes or bone (a minimum of 1 and a maximum 5 lesions will be irradiated), provided there is no significant overlap between the lesions. Patients should have RECIST 1.1 criteria measurable disease in addition to the lesion/s treated with radiation. If the site/s of radiation were previously radiated to high dose RT (>50Gy), there should be >6 month time interval between the last dose of radiation and the start of radiation. .

7. Have the ability to tolerate required radiotherapy-related procedures(eg: lie flat and hold position for treatment) as determined by the treating physician

8. Be willing and able to provide written informed consent for the trial and comply with the study visit requirements

9. Have measurable disease based on RECIST 1.1. (in addition to the lesion/s that will be treated with hypofractionated radiation therapy)

10. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.

11. Have a performance status of 0 or 1 on the ECOG Performance Scale.

12. Demonstrate adequate organ function as defined in below, based on screening labs should be performed within 10 days of treatment initiation.

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
- Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
- Serum creatinine CL>60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

  Males:

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

  Females:

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

13. Evidence of post-menopausal status OR negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

14. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

15. Female subjects of childbearing potential should be willing to use 1 method of highly effective birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 180 days after the last dose of study medication (Reference Section 7.1). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

16. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study therapy.

17. Patient is ≥ 5 years free of another primary malignancy, except: a) if the other malignancy is basal cell carcinoma or cervical carcinoma in situ or b) if the other primary malignancy is not considered clinically significant and is requiring no active intervention

4.2 Exclusion criteria

The subject ***must be excluded*** from participating in the trial if the subject:

1. Has a body weight ≤40kg at the time of enrollment

2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3. Has a target lesion/s for radiotherapy that is > 5 cm (> 50 cc) in greatest dimension

4. Has a target lesion/s in a region that previously received high dose RT (>50 Gy) demonstrating any of the following:
    a. carotid artery encasement (> 180 degrees)
    b. unprotected carotid artery (i.e. skin is directly over the carotid without intervening soft tissue, especially after prior neck dissection without a vascularized free flap) (a&b due to risk of carotid blow out)
    c. skin infiltration by tumor (due to risk of fistula)
    d. located in the larynx/hypopharynx primaries (due airway threat) treated with high dose radiation therapy (>50 Gy) within 6 months or less of trial enrollment

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

6. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:

    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)

    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication

7. Has received a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

8. Has received prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    -Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

-Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

9. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

10. Has known brain metastases or spinal cord compression unless the patient is stable (asymptomatic; no evidence of new or emerging brain metastases; and stable and off steroids for at least 14 days prior to start of study treatment). Following radiotherapy and/or surgery of the brain metastases patients must wait 4 weeks following the intervention and before initiating study treatment with imaging to confirm stability.

11. Has an active autoimmune disease requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study.

12. Has evidence of current interstitial lung disease (ILD) or pneumonitis or a prior history of ILD or pneumonitis requiring oral or intravenous glucocorticoids

13. Has an active infection requiring systemic therapy.

14. Requires therapeutic anticoagulation or has known active bleeding diathesis

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 180 days after the last dose of trial treatment.

18. Has received prior therapy with an anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

20. Has evidence of acute or chronic hepatitis B, or hepatitis C

21. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

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

23. Has a history of primary immunodeficiency or an allogeneic organ transplant

24. Has a history of hypersensitivity to durvalumab or tremelimumab excipient

25. Known history of previous clinical diagnosis of tuberculosis

26. Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, seizures

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3. Withdrawn patients will not be replaced.

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of durvalumab and or tremelimumab

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab + tremelimumab
- Any AE that meets criteria for discontinuation as defined in Section 10.3.
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- 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
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 13 cycles of durvalumab
- Grade ≥ 3 infusion reaction

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Subjects who are permanently discontinued from receiving investigational product will be allowed for safety per Appendix 2 or 3, 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.

4.4 Replacement of subjects

Replacement of Patients in Run in Phase

Patients who received <90% of the durvalumab and tremelimumab infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the phase I run in cohort and need to be replaced.

If a patient experiences a DLT in Cycle 1, study therapy may be discontinued following discussion and agreement between the Sponsor and Investigator.

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 solutions 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 10.0 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 or 25-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 20.0 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 (> 30kg in weight) 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 16 for a total of 13 doses. Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start 1 hour (+/- 5 mins.) after the end of tremelimumab infusion. The duration will be 1 hour(+/- 5 mins.) for each infusion. A 1 hour (+/- 5 mins.) 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 a minimum of 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. Radiotherapy is not required during retreatment, although it may be considered per the discretion of the treating physician.

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 (ie, 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 13 cycles).

During the retreatment period, patients (> 30kg) 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, for a total of 13 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).

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

5.2.3 Study drug preparation of durvalumab and tremelimumab

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. for patients > 30kg in weight.

In patients whose weight falls to 30kg or less dosing should be delayed (for up to a maximum of 2 treatment cycles) until their weight returns to 30kg or higher when dosing can be resumed at the next cycle. If the weight does not return to 30kg or higher after a maximum 2 cycle delay then dosing should be permanently discontinued). Patients whose weight is below 30kg should not be dosed as they would be exposed to endotoxin levels that exceed the USP specification limit).

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

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

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

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, 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. Add 30.0 mL of durvalumab (ie, 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion 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 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

If storage time exceeds these limits, a new dose must be prepared from new vials. The infusion solutions in the prepared final IV bag should be equilibrated to room temperature prior to administration.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab. Doses of 75 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 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. Add 3.8 mL (ie, 75 mg of tremelimumab) to the IV bag. In the event that a 50mg tremelimumab dose is required, add 2.5 mL (ie, 50 mg of tremelimumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Tremelimumab will be administered at room temperature (approximately 25°C) by controlled infusion 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 IV solution 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 (eg, 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 investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational products in accordance with the protocol and any applicable laws and regulations. Clinical supplies will be provided by AstraZeneca and affixed with a clinical label in accordance with regulatory requirements. Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

5.2.6 Disposition of unused investigational study drug

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

5.3 Radiation therapy

All subjects will be immobilized in a custom designed device in the appropriate position to isolate the index lesion. Radiotherapy treatment planning CT scans (with contrast, unless contraindicated) will be required to define the gross target volume (GTV) Clinical target volume (CTV) and planning target volume (PTV). The use of IV contrast is left to the discretion of the treating physician PET-CT and/or MRI imaging are preferred although not required to delineate volumes as accurately as possible. The treatment planning CT scan should be acquired with the subject in the same position and immobilization device, as for the treatment. Treatment planning will be performed using a 3D CT based treatment planning system. All tissues to be irradiated must be included in the CT scan. Planning CT scan will be obtained with a uniform slice thickness of less than or equal to 3 mm throughout and encompass the region of interest with sufficient margin for treatment planning.

All lesions with potential for respiratory motion should be evaluated by appropriate means including 4D CT scan and/or implanted fiducial marker(s). Respiratory motion management including but not limited to abdominal compression, active-breathing control (ABC), respiratory gating and fiducial marker tracking, will be employed for qualifying patients per standard clinical practice.

Daily image guidance will be employed for target localization. This is most commonly performed with volumetric imaging (cone-beam CT).

5.3.1 Radiotherapy Targeting and Treatment

HIGRT and SBRT have now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology (Potters 2004). This protocol will respect that guideline. The term stereotactic, for the purposes of this protocol, implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable "fiducial" markers. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that are indirectly referenced to the tumor (surrogates). This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation-producing device in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward a target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radiopaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (For example acquiring tomographic views of the tumor simultaneously with the treatment with a cone beam CT scan (CBCT)). Metallic "seeds" placed within the tumor will be allowed to constitute a fiducial so long as the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed).

5.3.2. Target Contouring

Gross Tumor Volume (GTV) is defined as all known gross disease encompassing the selected index lesion. The GTV will consist of the index lesion as visualized on CT +/- PET/CT, and/or MRI. Image fusion is encouraged when using multiple modalities to define the GTV.

Clinical Target Volume (CTV) will be the same as GTV for most cases. In case of uncertainty, GTV may be expanded to CTV by 2-3mm per clinician discretion.

Internal Gross Tumor Volume (IGTV) is defined for mobile index lesions at the discretion of the treating physician. For mobile index lesions, a 4-D CT scan will be acquired in order to account for the motion of the lesion during treatment. The IGTV will be defined as the union of the visualized index lesion on all gated CT data sets.

Planning Target Volume (PTV) will be defined as per convention for photon beam radiotherapy. A 3-dimensional margin of 3-5mm will be created on the CTV or IGTV (if available) to allow for daily set-up variance. For Proton beam radiotherapy, an additional range uncertainty is added during planning.

Organ at risk volume (OAR) is contoured as visualized on the planning CT or MR scan.

Planning organ at risk volume (PRV) is the OAR expanded for setup uncertainty or organ motion. The physician will contour the OAR. The dosimetrist will create the PRV by expanding the OAR by 1-3 mm, depending on the situation.

Pertinent Organs at Risk (OARs) in the index region are contoured as applicable to the region being treated by HIGRTor SBRT:

Spinal cord, Brain stem, Brachial plexus (roots & trunks), Cauda equina, Sacral plexus

Optic pathways – optic nerves, optic chiasm, Retina, Cornea

Carotid artery (Internal & common),

Cochlea & vestibular apparatus

Parotid and Sub mandibular glands

Skin (3-5 mm of body outline)

Larynx (infrahyoid supraglottis to bottom of cricoid. Only include the endolarynx within the cartilaginous framework

Other uninvolved mucosal structures eg: oral cavity & pharynx

Facial Bones : Mandible, Maxilla, temporal bone that pertain to index region

Esophagus

Heart and Pericardium

Lungs

Ribs

Trachea and Large/Central Bronchi

Bronchii – smaller airways

Liver

Stomach, Duodenum, Small Bowel

5.3.3. Radiation Treatment planning, dose fractionation and organs at risk specification

Computer based planning & quality assurance (QA) will be performed using our standard institutional HIGRT and SBRT guidelines, to deliver HIGRT or SBRT to the index lesion(s), including static 3D coplanar and/or non-coplanar beam arrangements as well as dynamic conformal arcs. Corrections for tissue heterogeneity, and robustness analysis (for Proton therapy) will be made. Treatment planning may be performed with 3D-CRT, IMRT, VMAT or, Proton beam RT (Pencil beam RT or Uniform scanning).

3D coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, >/= 5-10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for lesions that are in very close proximity to a critical OAR to produce appropriately protective concave dose distributions with a steep dose gradient between the target lesion and the OAR.

For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized.

Proton beam planning is performed with 2-4 beams. In order to obtain acceptable coverage, field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception should be when observing the minimum field dimension of 3.5 cm when treating small lesions (see above).

Radiotherapy prescription: The dose prescription will be as follows: 24 Gy given in 3 fractions to PTV (80-95% IDL) delivered at 8 Gy per fraction every other day. however, a dose reduction to 6 Gy per fraction will be permitted if 8 Gy is not achievable due to dose constraints.

Dose Uniformity: 95% of the planning target volume (PTV) should be covered by the prescription dose (PTV V95%RX = 100%) and 99% of the planning target volume (PTV) should receive a minimum of 90% of the prescription dose (PTV V99%RX > 90%). 99% of the CTV should receive a minimum of 98% of the prescribed dose (CTV V99%RX >98%); however, higher isodoses (hotspots) of > 105% of prescribed dose must be manipulated to occur within the target and not in adjacent normal tissue.

Dose rate: For the purpose of this study, dose rate utilized will be that which is commissioned by the manufacturer and the medical physics group for external beam radiotherapy delivery by

the treating institution. There will be no special dose rate modifications required for this study.

Critical Organ Doses: For de novo cases (no prior RT) all the following critical organ dose-volume limits will be respected.

The following PRV dose constraints may be used as guidelines: (adopted from Timmerman RD. An overview of hypofractionation. Seminars of Radiation Oncology 2008 Oct;18(4):215-222 and Lo SS et al. Serious Complications Associated with Stereotactic Ablative Radiotherapy and Strategies to Mitigate the Risk. Clinical Oncology 2013 Jun;25(6):378-387).

Spinal cord PRV max 20 Gy

Spinal cord max 18 Gy

Brain stem max 22.5 Gy, 18 Gy (< 0.5cc)

Optic chiasm max 15 Gy, 12 Gy (< 0.2cc) (for bilateral blindness risk)

Ipsilateral Optic nerve max 18 Gy, 15 Gy (< 0.2cc)

Contralateral optic nerve max 12 Gy, 10 Gy (< 0.5cc)

Carotid artery max 15 Gy, (V12 Gy to < 30% of carotid volume)

Brachial plexus max 24 Gy, 20 Gy (< 3cc)

Esophagus* max 24 Gy, 17 Gy (< 5cc)

Heart/Pericardium max 27 Gy, 24 Gy (< 15cc)

Trachea* max 24 Gy, 15 Gy (< 4cc)

Bronchus max 24 Gy, 15 Gy (< 1cc)

Ribs max 27 Gy, 24 Gy (< 5cc)

Skin max 27 Gy, 24 Gy (<10cc)

Lung (Right & Left) – V20 < 10%, 11.4 Gy (< 1000cc) 10.5 Gy (< 1500cc)

Great vessels, non-adjacent wall max 27 Gy, 24 Gy (< 10cc)

Liver – spare >700cc to </=17.1 Gy

Stomach – max 22.2 Gy, 16.5 Gy to < 10cc

Colon – max 27 Gy, 24 Gy (<20cc)

Renal cortex (right and left) 15 Gy (>65%), 14.4 Gy (200cc)

Rest of OARS = ALARA

* avoid circumferential radiation

For re-irradiation cases, the above constraints do not apply. The treating physician's discretion would be used in such cases based on the previous dose exposure to various OARs as determined from the prior treatment plan and clinical goals.

Planning Priorities and Dose specifications

Every attempt will be made to successfully satisfy all of the planning goals and OAR criteria without deviation. All critical organ dose-volume limits will be respected. As far as possible, all OAR constraints will be met while providing full coverage to the PTV. In some cases, it may not be possible to meet all planning goals. In such cases, OAR constraints and PTV coverage will be balanced per the discretion of the treating physician. Brain stem, optic nerves, optic chiasm, spinal cord, brachial plexus, cauda equine and sacral plexus dose constraints must be respected over PTV coverage. In cases of other OAR constraints, which are not well validated, PTV coverage and OAR constraints must be balanced per clinical practice at the discretion of the treating physician.

Image Guidance:

Image guided RT (IGRT) is required with physician review per institutional QA requirements before each treatment is delivered. Cone beam CT will be matched to target volume to be treated and bony anatomy or other defined fixed fiducials. If CBCT is unavailable, orthogonal pair KV imaging matched to stable bony anatomy closest to PTV is acceptable.

6. TREATMENT PLAN

The Trial Flow Chart – in Protocol Synopsis, summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or AstraZeneca for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations

6.1 Subject enrollment

6.1.1 Procedures for enrollment

Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the

subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

Prior and Concomitant Medications Review

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement.

Disease Details and Treatments

Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the

first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

6.1.2 Procedures for handling subjects incorrectly enrolled patients

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

6.2. Dosage and Administration

The treatment to be used in the run in phase of this trial for patients > 30kg is outlined in the Table below:

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
1. Durvalumab	1500 mg	Q4 weeks	IV infusion	Maximum of 13 doses
2. Tremelimumab	75mg	Q4 weeks	IV infusion	Maximum of 4 doses

If 2 or more DLTs (defined in Section 6.4) are observed in the run-in phase, the following treatment will be used for the remaining 14 patients to be treated on the clinical trial protocol:

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
1. Durvalumab	1500 mg	Q6 weeks	IV infusion	Maximum of 9 doses
2. Tremelimumab	75mg	Q6 weeks	IV infusion	Maximum of 3 doses

Patients who experience a DLT in the run in phase, will have dose interruptions/modifications as outlined in Appendix 1.

6.3 Dose Escalation Decision Rules

There will be no dose escalations performed on this study.

6.4 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated during the run in phase consisting of the first 6 patients enrolled in this trial. The period for evaluating DLTs will be from the time of first administration of durvalumab or tremelimumab until 28 days (cycle 1). Adverse event monitoring will continue for these subjects throughout the course of their treatment (beyond cycle 1) as outlined in the Schedule of Study Assessments, these adverse events will include potential XRT related toxicities. Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
    - Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
    - Concurrent vitiligo or alopecia of any AE grade
    - Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
    - Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility

- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

- Prolonged delay (>2 weeks) in initiating cycle 2 due to treatment-related toxicity
- Grade 5 toxicity, i.e. death

Dose modification/delays according to Section 6.5.1 and Appendix 1 will apply to the patients who experience DLTs in the run in phase.

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

6. 5 Dose Modification and Toxicity Management

6.5.1 Durvalumab and tremelimumab

For adverse events (AEs) that are considered at least partly due to administration of durvalumab (or durvalumab and tremelimumab for cycles 1-4) 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 durvalumab and tremelimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab and tremelimumab (see Appendix 1).
- 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.(see Section 4.3)

Following the first dose of durvalumab or tremelimumab, subsequent administration of durvalumab or tremelimumab can be modified based on toxicities observed (see Appendix 1).

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 Appendix 1.

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 v4.03.

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:

Female patient of child-bearing potential

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 1) 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. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point

should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide 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. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table).

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 2. Note that some contraception methods are not considered highly effective (eg. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills

where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 2. Highly effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Etonogestrel implants: eg, Implanon or Norplan • Intravaginal device: eg, ethinylestradiol and etonogestrel • Medroxyprogesterone injection: eg, Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

[a] This is also considered a hormonal method

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 1) 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 (ie, 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 1) 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 3. 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 (eg, 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.

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). Restricted, prohibited, and permitted concomitant medications are described in the following sections. Refer to Appendix 1 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 6.2.2.

7.2.2Excluded 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. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

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 (ie, 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 4. 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, eg, radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, 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. (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.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP during the study

Prohibited medication/class of drug:	Usage:
VEGF inhibitors such as sunitinib, sorafenib and bevacizumab	Should not be given 90 days prior to first dose of investigational drug and with 30 days after last dose of investigational drug

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

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 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study.

Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Archived tissue or tumor biopsy
- Review of prior/concomitant medications
- Imaging by CT/MRI
- Clinical laboratory tests for:
    - Hematology (see Table 3)
    - Clinical chemistry (see Table 4)
    - TSH with reflexive free T4
    - Coagulation (PT, aPTT, INR)
    - Creatinine Clearance
    - Serum or urine pregnancy test (for women of childbearing potential only)
    - Urinalysis (see Table 7)

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.

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 completing all13 cycles, 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.

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 2.

Assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in APPENDIX 3.

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. 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, triplicate 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.

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 (eg, 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 Per standard clinical practice.

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.

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) OR
    - Serum beta-human chorionic gonadotropin (at screening only)
- Thyroid Stimulating Hormone
    - free T4 only if TSH is abnormal

Table 5. 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 6. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

Table 7. 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

8.3 Biological Sampling Procedures

8.3.1 Research Blood Collection

Blood will be collected for research purposes on three occasions: at baseline, prior to the second dose of durvalumab and tremelimumab and prior to the 4th dose of durvalumab and tremelimumab. Blood will be separated into cellular and serum components for preservation and batch analysis. Flow cytometric evaluation of CD3, CD4, CD8, CD14, PD-1, PD-L1, PD-L2 on peripheral blood mononuclear cells.

Specimen Requirements: Submission for flow cytometry

- A 5-10 mL specimen of peripheral blood in a lavender- (EDTA) or green- (sodium heparin) tube is acceptable for each draw.
- Storage/Transport Temperature: Specimens can be transported with a cold pack or wet ice, but do not fix or freeze specimens.
- Unacceptable Conditions: Frozen specimens, specimens greater than 48 hours old, specimens fixed in formalin for flow cytometry
- Address for shipping specimens:

Attn: Katy Dougherty, Hematopathology Lead

Seattle Cancer Care Alliance

Hematopathology Laboratory G7800

825 Eastlake Ave E.

Seattle, WA 98109

8.3.2. Correlative tissue collection

All patients will be required to submit archival tissue as part of study participation. In patients who do not have archival tissue, a pretreatment tumor biopsy will be performed, unless deemed contraindicated by the treating physician. These samples will be submitted centrally for immunohistochemical expression studies involving proteins in the PD-1 family as well as CD3,

CD69 and FOXP3. Acceptable archival tissue for correlative studies include formalin fixed paraffin embedded tissue collected within 3 years of study enrollment. Patients who do not have acceptable FFPE tissue will be required to undergo a study related biopsy to obtain fresh tissue. In cases where biopsies yield insufficient tissue for both tumor slice culture (TSC) and PDL1 testing, TSC testing will take priority. Any tissue not used for tumor slice culture will be submitted for PDL1 testing.

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 reproducibility 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.

- 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. Samples from fine needle aspirates (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)
- Site identifier
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh 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

<u>Preparing Stored samples for testing</u>

- 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

Fresh tumor biopsies for tumor slice culture

Patients who do not have suitable archival tissue will be consented for fresh tissue biopsies. Dr. Venu Pillarisetty's lab will oversee the collection of fresh tissue during this biopsy. Tissue will be collected for tumor slice culture (TSC) preparation as described below. In cases where biopsies yield insufficient tissue for both TSC and PDL1 testing, TSC testing will take priority. Any tissue not used for tumor slice culture will be submitted for PDL1 testing.

TSC Preparation

Fresh treatment biopsy tissue in excess of that required for central IHC will be mounted and sliced (250 μm) using a Leica vibrating microtome. This tissue will be placed in 24-well plates in an air-liquid interface culture system using media optimized by our group for TSC.

Experiment #1 – Immune cell populations

TSC will be cultured for 1 to 6 days with control antibody, DMSO control, durvalumab (dose to be determined) alone, tremelimumab(1 μM) alone, or a combination of both drugs.

IHC for CD4, CD8, FOXP3, CD68

When adequate tissue is available for replicates, we will perform flow cytometry on enzyme-digested, disaggregated slices to measure:

Macrophage phenotype (CD68, HLA-DR, CD163, CD115, CD206)

T cell phenotype (general): CD3, CD4, CD8, CD25

T cell memory phenotype (CD45RO, CD127, CD28, CD27, CD62L, CCR7)

T cell inhibitor phenotype (PD-1, CTLA-4, LAG3, TIM3)

Tumor immune related markers (PD-L1, class I MHC, HLA-DR)

Experiment #2 – Induction of CD8+ T cell function

Upon completion of each culture period after drug treatment, slices will be treated with SR-FLICA caspase 3/7 assay reagent (Immunochemistry Technologies) for 1 hr, fixed, and then stained with DAPI prior to imaging by confocal microscopy to measure apoptosis. Fixed tumor slices will then be paraffin embedded and sectioned. IHC will be performed for CD8 and Ki67 (to measure proliferation) or granzyme B (to measure cytotoxic activity) or cleaved caspase 3 (to measure apoptosis). Number of positive cells for each marker will be determined.

Experiment #3 – Correlation of induction of cytotoxic T cell function with PD-L1 expression

We hope to have access to the centrally determined PD-L1 expression so that we will be able to correlate our CD8+ T cell functional data with induction of CD8+ T cell function.

Experiment #4 – Correlation of induction of cytotoxic T cell function with clinical response

We will use multivariate statistics to test the hypothesis that the degree of immune checkpoint inhibition-triggered CD8+ T cell activation and carcinoma cell death in TSC predicts response in our ongoing clinical trial.

Experiment #5 – Rescue of drug-refractory CD8+ T cell activation

Biopsies from patients with lack of clinical response will be placed in TSC and treated with combinations of durvalumab and tremelimumab and monoclonal antibodies designed to block additional immune checkpoints (GITR, LAG-3, TIM-3, CTLA-4), as this strategy may overcome T cell exhaustion.(Lu et al., 2014)

Experiment #6 – Correlation between T cell infiltrate and immunosuppressive signals

IHC of tumor tissue for cellular subtypes (CD3, CD4, CD8, FOXP3, CD68) and immunosuppressive molecules (PD-1, PD-L1, TIM-3, LAG-3, CTLA-4, IL-10, TGF-beta1, IDO, FASL). We will use multivariate statistics to correlate T cell infiltrate density and level of immunosuppressive signaling. Furthermore, we will be able to confirm whether the tumors

fall into their expected category of level of T cell infiltration, as we believe that the immunophenotype is more important than traditional histology in determining response to immune checkpoint inhibition.

Experiment #7 – CD8+ T cell suppression

The proliferation of CD8+ TIL from TSC (cultured with or without exogenous IL-2 +/- CD3/CD28 beads) will be measured in two ways: directly by Ki67 staining, and indirectly by treating the TSC with BrdU and then subsequently staining for it. In both cases TSC will be fixed, embedded and double stained after 1 to 6 days in culture to determine what percentage of CD8+ T cells are cycling. Duplicate slices will be digested with collagenase-DNAse-hyaluronidase cocktail in rotating flasks to obtain a single-cell suspension. CD8+ T cell proliferation and activation state, as well as macrophage polarization, will be tested using a multi-color flow cytometry panel. We will correlate these data with those from Experiment #1 to determine if high-level expression of multiple immunosuppressive signals has functional consequences in the TSC.

Experiment #8 – Combination immune checkpoint inhibition

TSC will be cultured for 1 to 6 days with control antibody or durvalumab (dose to be determined).

Upon completion of each culture period, slices will be treated with SR-FLICA caspase 3/7 assay reagent (Immunochemistry Technologies) for 1 hr, fixed, and then stained with DAPI prior to imaging by confocal microscopy to measure apoptosis. Fixed tumor slices will then be paraffin embedded and sectioned. IHC will be performed for CD8 and Ki67 (to measure proliferation) or granzyme B (to measure cytotoxic activity) or cleaved caspase 3 (to measure apoptosis).

To determine whether immune checkpoints in fact inhibit the proliferation of T cells in the TSC, each of the known checkpoint molecules will be inhibited, either by antibody (PD-1, TIM-3, LAG-3, CTLA-4, IL-10, TGF-beta1, FASL) or using a small molecule (IDO) in the organotypic cultures. If the checkpoint is suppressing cytotoxic T cell proliferation, we would expect to see increased Ki-67 staining, and increased BrdU uptake by CD8+ T cells in the TSC. In tumors that express multiple checkpoint molecules, inhibition of several pathways

may be required to overcome T cell functional exhaustion; in these cases, the effects of combination of checkpoint inhibitors on T cell proliferation will be investigated. Assessment of T-cell exhaustion and rescue will be based on the stimulated expression of IFN□. Single-cell suspensions from tumor slices will be treated with Golgi plug and stimulated with CD3/CD28 beads (for TCR and costimulation) or PMA/ionomycin (bypassing TCR signaling) prior to performing intracellular cytokine staining for flow cytometry. The proportion of IFN□-expressing CD8+ T cells in the TSC will be compared between treatment and control samples. For all immunohistological and flow cytometric analyses, a minimum of 100 cells of interest will be scored for each endpoint. Results between treated and control groups will be analyzed by t-test and ANOVA. Data will be analyzed across tumors with relation to level of T cell infiltration and immunosuppressive signal expression.

8.3.3 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:

- 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

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 Progression free and Overall survival

Data on disease progression by RECIST criteria, and patient death will be recorded and used to calculate PFS and OS. Patients who have discontinued study therapy due to disease progression, toxicity, or withdrawal of consent will continue to be followed to collect data for this endpoint.

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 is familiar with the content of this section.

10. 1 Safety Parameters

10.1.1. 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 (ie, 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 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 etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with durvalumab 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:

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 Appendix 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)

Immune-mediated hepatic function abnormalities include transaminitis, hepatitis and hepatotoxicity of any grade on concurrent tests. 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 (eg, 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 Appendix 1.

Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

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.

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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, **Error! Reference source not found.**). 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 (eg, 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 (**Error! Reference source not found.**). 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 (eg, 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

An investigator who is a qualified provider will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. Any adverse event which

changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

The determination of the likelihood that durvalumab and or tremelimumab caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.

The following components are to be used to assess the relationship between durvalumab and/or tremelimumab and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely that durvalumab and/or tremelimumab caused the adverse event (AE):

- Is there evidence that the subject was actually exposed to durvalumab and tremelimumab such as: reliable history, acceptable compliance assessment expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
- Did the AE follow in a reasonable temporal sequence from administration of durvalumab and tremelimumab?
- Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
- Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

10. 3 Recording of adverse events and serious adverse events

Adverse events will be recorded 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)

- 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 of hospitalization and discharge, if applicable
- Date of death and probable cause, if applicable
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

- Causality assessment in relation to palliative hypofractionated radiation therapy

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 administration of the first dose of investigational drug, 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 CRF. 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.

NOTE TO AUTHOR: For trials conducted in the United States, the following must be included (similar language must be included , referencing the appropriate health authority and reporting mechanism, for studies conducted outside of the United States). Note that all serious or unexpected adverse events must be reported to AstraZeneca regardless of the country where the study is conducted:

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-16-11857)

***** 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 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 durvalumab safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

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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

Maternal exposure

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

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

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 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.

11.0 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

All patients enrolled in the study, including those who were replaced in the run-in phase (see Section 4.4) will be included in the analysis of toxicity and efficacy.

11.2 Methods of statistical analyses

11.2.1 Safety Analyses

Safety and tolerability is the primary endpoint of this study, and all patients enrolled (including those replaced in the run in phase) will be assessed for this endpoint. Adverse events will be recorded and graded based on CTCAE v. 4, and their relationship to the experimental agents reported.

11.2.2 Efficacy Analyses

All patients enrolled in the study (i.e. the initial 6 patient cohort, and the additional 14 patient expansion) will be included in the efficacy analyses. Clinical responses to the combination of durvalumab, tremelimumab and hypofractionated radiation will be based on RECIST 1.1 criteria. Oncologic outcome endpoints such as progression free and overall survival will be calculated from the date of study enrollment, until disease progression or death from any cause, respectively. Survival estimates will be calculated using the Kaplan-Meier method.

11.2.3. Exploratory Analyses

Exploratory endpoints of this study include correlative work performed on research serum and tissue samples. These are detailed in Section 8.2

11.2.4 Interim analyses

No interim analysis is planned for this study.

11.3 Determination of sample size

There are multiple ongoing studies in various tumor types exploring the activity of durvalumab and tremelimumab. In a published report of the combination in patients with advanced NSCLC treated on a phase Ib study, Grade 3-4 toxicity was observed in 17% of patients. Similarly, in single institution reports of SBRT with the monoclonal antibody, grade 3 or higher toxicity was reported in 6-16% of patients. With 20 patients, toxicity rates can be estimated to within 22% with 95% confidence. Any toxicity with at least 10% prevalence has at least an 87% chance of being observed. With these properties, this design, allows us to reasonably exclude a clinically significant increase in toxicity with the addition of radiation therapy to the durvalumab and tremelimumab combination as defined by the upper bound of the confidence interval.

The response rates to dual CTLA and PDL1 blockade and radiation therapy after prior immunotherapy are unknown. If objective responses are demonstrated, or encouraging progression free survival is observed in the 20 patients enrolled on the study, it would merit further investigation in a larger study powered to examine efficacy endpoints

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 Subject data protection.

12.2 Ethics and regulatory review

The protocols will be approved and reviewed by the Cancer Consortium Scientific Review Committee (SRC) and the Institutional Review Board (IRB). The protocol once activated will be reviewed at least annually by both institutional entities.

12.3 Informed consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable

opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

12.4 Changes to the protocol and informed consent form

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Cancer Consortium IRB and Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

12. 5Audits and inspections

The study will be audited and inspected by the Cancer Center Consortium.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

All investigators on the protocol will receive formal training in the ethical conduct of human research. **I**nstitutional support of trial auditing is provided in accordance with the **C**ancer **C**onsortium's data and safety monitoring plan

13.2 Monitoring of the study

13.2.1 Source data

The Fred Hutchinson/University of Washington Consortium Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study in accordance with the Cancer Consortium's Data Safety Monitoring Plan.

13.3 Study timetable and end of study

The end of the study is defined as the last visit of the last patient undergoing the study. Either AstraZeneca or the Investigator may terminate the entire study prematurely if concerns for safety arise within this study or other durvalumab studies.

14. DATA MANAGEMENT

The Protocol Director, or her designees, will prepare and maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to analyze the study data. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

All data required by the trial will be entered onto paper and electronic case report forms. Any corrections to data required into the paper case report forms must be made in such a way that the original entry is not obscured. Only designated study staff will enter data for study participants after study visits. Case report forms will be checked against source document data by study staff.

Patient records will be kept in a secure location at the University of Washington accessible only to research authorized personnel. The patient identity will be kept as confidential as possible as required by law. Except as required by law, the patient will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Study subjects will be assigned an ID code. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, the patient identity will not be disclosed. The patient's personal data which may be included in the investigator's database shall be treated in compliance with all applicable laws and regulations.

Trial oversight will be carried out by the protocol director, Dr. Cristina Rodriguez, and her research staff. They will meet weekly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

14.1 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 8. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab (MEDI4736)	50 mg/mL solution for infusion after dilution	AstraZeneca/MedImmune
Tremelimumab	20mg/mL solution for infusion after dilution	AstraZeneca/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
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APPENDIX 1

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) 19 August 2016 Version

Dose Modifications	Toxicity Management
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/study 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/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **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 regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.	It is recommended that management of irAEs follows the guidelines presented in this table: – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections). – 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 (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) 19 August 2016 Version

Dose Modifications	Toxicity Management
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	

(i) AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; irAE Immune-related adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	**Any Grade**	General Guidance	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical 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 modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider pulmonary and infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-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 [eg, 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 (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Enterocolitis	**Any Grade**	General Guidance	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or 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 (stool frequency of <4 over baseline per day)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (stool frequency of 4 to 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.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		• If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	– Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 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 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks. **Caution:** it is 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 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (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:** – 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 to 5 days of IV

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × ULN)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	**For Grade 3:** 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 to 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 Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 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.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		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 >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	of cancer-related infections [Category 2B recommendation]).[a]
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – 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 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (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.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – 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 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		• 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.	hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 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 such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For 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 4:** 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 the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for	General Guidance	**For Any Grade:** – Consult endocrinologist. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	defining the CTC grade/severity)		changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient 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.	**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.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		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. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 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 resumed once event stabilizes and after completion of steroid taper.	**For Grade 3 or 4:** – Consult endocrinologist. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and	**For Grade 2:** – Discuss with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		after completion of steroid taper.	immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For 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 4:** Permanently discontinue study drug/study regimen.	**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 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4	**For 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 Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening 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. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

(ii) [a] ASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by Michael Postow MD.

(iii) [b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

(iv) AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; irAE Immune-related adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PCP ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

(v) CTCAE Common Terminology Criteria for Adverse Events; IM Intramuscular; IV Intravenous; NCI National Cancer Institute.

Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 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.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

(vi) 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."

(vii) AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Appendix 2 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	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
ECOG performance status	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
Serum chemistry	X							
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 8-12 weeks relative to the date of **first infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. 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 8-12 weeks until confirmed PD by RECIST 1.1 by investigational site review. Upon confirmed PD, scans should be conducted according to local standard clinical practice							

Appendix 3 Schedule of study procedures: follow-up for subjects who have discontinue 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	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
ECOG performance status	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							
Serum chemistry	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** until MEDI4736 is stopped. For subjects who **discontinue MEDI4736 following confirmed progression**, **scans should be conducted according to local clinical practice**.							