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WINDOW OF OPPORTUNITY PHASE II STUDY OF MEDI4736 OR MEDI4736 + TREMELIMUMAB IN SURGICALLY RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA

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PROTOCOL SYNOPSIS

Clinical Protocol ESR-14-10744

Study Title: WINDOW OF OPPORTUNITY PHASE II STUDY OF MEDI4736 OR MEDI4736 + TREMELIMUMAB IN SURGICALLY RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA
Protocol Number: ESR-14-10744
Clinical Phase: II
Study Duration: 24 months
Investigational Product(s) and Reference Therapy: MEDI4736 will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. Tremelimumab is supplied as a sterile IV solution in 20 mL clear glass vials with a rubber stopper and aluminum seal.
Research Hypothesis: Our hypothesis is that neoadjuvant therapy with anti-PD-L1 monoclonal antibody MEDI4736 in combination with anti-CTLA-4 monoclonal antibody tremelimumab will result in favorable alterations of the intratumoral immunologic environment in subjects undergoing resectional surgery for malignant pleural mesothelioma (MPM).
Objectives: **Primary Objectives:** The primary objective of this study will be comparison of the ratio of intratumoral cytotoxic T cells to regulatory T cells (CD8/Treg) before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy. **Secondary Objective(s)**: The secondary objectives of this study are: 1) Comparison of the percentage of inducible T-cell co-stimulator (ICOS) positive intratumoral CD4 T cells before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy. 2) Comparison of tumor tissue expression (Ventana assay) of programmed death-ligand 1 (PD-L1) before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy.

3) Comparison of the ratio of the intratumoral CD8/Treg ratio in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone , and separately compare to untreated patients.
4) Comparison of the percentage of inducible T-cell co-stimulator (ICOS) positive intratumoral CD4 T cells in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone, and separately compare to untreated patients.
5) Comparison of tumor tissue expression (Ventana assay) of programmed death-ligand 1 (PD-L1) in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone, and separately compare to untreated patients.
6) Comparison of overall survival in patients treated with either MEDI-4736 alone or MEDI-4736 plus Tremelimumab with historical untreated controls. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.
7) Comparison of recurrence-free survival in patients treated with either MEDI-4736 alone or MEDI-4736 plus Tremelimumab with historical untreated controls. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.

Study Design:

Subjects with MPM will undergo surgical mediastinal lymph node biopsy (cervical mediastinoscopy) and simultaneous surgical biopsy of the pleural tumor by thoracoscopy, at which time tumor tissue (at least 2 g) and peripheral blood will be collected for the study. These procedures are performed as our standard of care in the treatment of these subjects. The subject will be randomized. Three days to three weeks after the biopsy, 20 evaluable subjects (if tissue obtained) will be randomly treated with either MEDI-4736 alone (15 mg/kg once intravenously) (n=8) or MEDI-4736 (1500 mg once intravenously) plus tremelimumab (75 mg once intravenously) (n=8), or a control group (n=4) in a randomized controlled study design. There will be two treatment arms (MEDI4736 only and combination MEDI4736+tremelimumab) and one untreated arm (control). Randomization, stratified by receiving previous chemotherapy or not, will be performed and will help to minimize patient selection biases between three arms. Subjects under 30 kg will be treated with weight-based dosing for both MEDI4736 and Tremelimumab combination therapy. These patients are excluded from fixed based dosing to limit endotoxin exposure from the drug preparations. One to six weeks after the infusion, subjects will undergo resectional surgery, including extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D), at which time the tumor will be removed (typically 200-1000 g) and obtained for study. Four patients that do not undergo treatment with MEDI-4736 or tremelimumab will be included as controls. Blood will be obtained after the induction of general anesthesia for both the thoracoscopy procedure and the EPP or P/D resectional procedure, as is routinely done in these procedures. The sixth rib will be obtained at the time of the resection. After the removal of the tumor, our standard protocol includes intraoperative heated chemotherapy using a lavage of intracavitary cisplatin in the presence of conserved renal function (Sugarbaker et al., 2013, 2014; Richards et al., 2006).

Tumor tissues obtained either by thorasoscopic biopsy or by resectional surgery will be evaluated by time-of-flight mass spectrometry (CyTOF) to determine intratumoral CD8/Treg ratios and percentage of ICOS positive CD4 T cells, and by immunohistochemistry (Ventana assay) to determine the tissue expression of PD-L1. These variables will be compared before and after treatment (changes within the same patient tumor), or between treatment groups (MEDI-4736 alone, MEDI-4736+tremelimumab, untreated) following treatment. Additional hypothesis-generating analyses will include a comprehensive systems based evaluation of the intratumoral immune cell population composition and phenotype phenotype [e.g., dendritic cells, macrophages, myeloid derived suppressor cells (MDSC), neutrophils, T-cell subsets, natural killer (NK) cells, and B cells], and immune-related gene expression using the nanostring system within the tumors, blood, and bone marrow of patients in all treatment groups.

Number of Centers: 1

Number of Subjects: 20

Study Population:
Subjects aged 18 years or older with resectable MPM

Inclusion Criteria:

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
2. Age $\geq$ 18 years at time of study entry
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
4. Adequate normal organ and marrow function as defined below:
   - Hemoglobin $\geq$ 9.0 g/dL
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L ($\geq$ 1500 per mm^3)
   - Platelet count $\geq 100 \times 10^9$/L ($\geq$100,000 per mm^3)
   - Serum bilirubin $\leq$ 1.5× institutional upper limit of normal (ULN)AST <3.0
   - Creatinine clearance >50mL/miN
   - Aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 2.5 \times$ ULN ($\leq$ 5 × ULN if documented liver metastasis are present);
   - Serum creatinine $\leq$ 2.0 mg/dL or calculated creatinine clearance $\geq$ 50 mL/min as determined by the Cockcroft-Gault equation;

Males:

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

Females:

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

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

6. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

7. Surgically resectable MPM with no disease extension beyond the ipsilateral hemithorax

8. Planned resectional surgery for MPM [extrapleural pneumonectomy (EPP) or pleurectomy and decortication (P/D)]

9. Any MPM histology (epithelial, mixed, sarcomatoid)

   a. N0 or N1 nodal disease, as present on preoperative chest CT and/or PET/CT

   b. N2 nodal disease if no progression after 2 cycles of standard chemotherapy. Progression will be considered if additional N1 or N2 disease develop during chemotherapy.

Exclusion Criteria:

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

2. Participation in another clinical study with an investigational product during the last 3 months

3. Any previous treatment with a PD1 or PD-L1 inhibitor, including MEDI4736

4. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 30 days prior to the first dose of study drug, and 30 days prior

	to the first dose of study drug for subjects who have received prior TKIs [e.g., erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C).
5.	Current or prior use of immunosuppressive medication within 28 days before the infusion with MEDI4736 or MEDI4736 + tremelimumab and through 90 days post infusion, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
6.	Any unresolved toxicity (>CTCAE grade 2) from previous anti-cancer therapy.
7.	Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
8.	Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
9.	Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
10.	History of primary immunodeficiency
11.	History of allogeneic organ transplant
12.	History of hypersensitivity to MEDI4736 or any excipient
13.	History of hypersensitivity to tremelimumab or the combination of MEDI4736 + tremelimumab
14.	Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
15.	Known history of previous clinical diagnosis of tuberculosis
16.	History of leptomeningeal carcinomatosis
17.	Receipt of live attenuated vaccination within 30 days prior to study entry or within 6 months of receiving MEDI4736 or MEDI + tremelimumab

18.	Receipt of drugs with laxative properties and herbal or natural remedies for constipation within 90 days of receiving MEDI4736 or MEDI + tremelimumab
19.	Receipt of sunitinib within 3 months of receiving tremelimumab
20.	Female subjects who are pregnant, breastfeeding, or male or female subjects of reproductive potential who are not employing an effective method of birth control
21.	Any condition that, in the opinion of the investigator, would interfere with the evaluation of the study treatment or interpretation of subject safety or study results
22.	Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation, and/or corticosteroids.
23.	Subjects with uncontrolled seizures
24.	N3 nodal disease
25.	History of interstitial lung disease/pneumonitis
26.	No tissue is obtainable at the time of thoracoscopy.
27.	Intraabdominal malignancy discovered at laparoscopy and proven pathologically, or nodal disease discovered at mediastinoscopy (N2 or N3 disease) and proven pathologically

Investigational Product(s), Dose and Mode of Administration:
MEDI4736, 15 mg, IV infusion once prior to resection

Or: Subjects will be administered MEDI4736 (1500 mg intravenously) + tremelimumab (75 mg intravenously) once during the study.

Subjects under 30 kg will be treated with weight-based dosing for both MEDI4736 and Tremelimumab combination therapy. These patients are excluded from fixed based dosing to limit endotoxin exposure from the drug preparations.

Study Assessments and Criteria for Evaluation:

Safety Assessments:
On the infusion day with MEDI4736 or MEDI4736 + tremelimumab, we will conduct clinical chemistry, hematology, and vitals. Subjects will be followed for 90 days after the last dose for safety to monitor any AEs, SAEs, etc.

Efficacy Assessments:

PRIMARY ENDPOINTS

1) Intratumoral CD8/Treg ratio determined by CyTOF.

SECONDARY ENDPOINTS

1) Percentage of ICOS+ CD4 T cells will be determined by CyTOF in blood, tumor, and bone marrow
2) PD-L1 expression will be determined in tumor tissue by IHC (Ventana assay); PD-L1 will also be determined on immune cell subsets by CyTOF in blood, tumor, and bone marrow.
3) NanoString gene expression arrays will be used to compare the gene expression of 300 immune-related genes in frozen tumor tissue obtained preoperatively and postoperatively.
4) Overall and recurrence-free survival survival will be measured according to our usual routine follow-up protocol and compared with historical controls. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.
5) A comprehensive evaluation of immune cell composition and phenotype will performed in preoperative and postoperative tumor tissue and peripheral blood, as well as bone marrow. **Appendix C** outlines the complete CyTOF panel that will be used for each individual specimen. Substudies will include:
   a. Changes in T-cell subset (i.e., CD4, CD8, FoxP3) frequency and memory and activation phenotype (i.e., CD25, CD127, CD45RA, CD62L, CCR4, CCR6, Tim1).
   b. Changes in the T-cell polarization state (intracellular interferon-gamma, TNF-alpha, IL-17, IL-2).
   c. Changes in myeloid cell composition: dendritic cell, macrophage, MDSC, neutrophil (i.e., HLA-DR, CD11c, BDCA-1, BDCA-2, BDCA-3, BDCA-4, CD68, CD163, CD206, CD66b, CD15).
   d. Changes in NK cell and NK T-cell composition (i.e., CD56, CD3, V224, Vbeta1)

   For all experiments requiring tissue, whereas relatively large tissue samples are generally obtainable from both pre-resection biopsies performed by thoracoscopy, and at the time of tumor resection, our experiments will be prioritized as follows:
   1) CyTOF
   2) IHC
   3) Gene expression

Statistical Methods and Data Analysis:

There will be two treatment arms (MEDI4736 only and combination MEDI4736+tremelimumab) and one untreated arm (control). Randomization, stratified by receiving previous chemotherapy or not, will help to minimize patient selection biases between three arms. Preliminary tests will be performed to assess whether our data is normally or non-normally distributed. Patient characteristics will be summarized descriptively. Baseline characteristics will be compared by treatment assignment. For our primary objective that compares outcome variable in tissues before and after treatment with combination MEDI4736 and tremelimumab, we will use a paired t-test in log-transformed ratio of intratumoral cytotoxic T cells to regulatory T cells (CD8/Treg) before and after the treatment. In our secondary objective numerous variable comparisons are made between tumor tissues from untreated patients with from patients undergoing treatment with either MEDI4736 or MEDI4736 + tremelimumab, and between tumor tissues from patients undergoing treatment with MEDI4736 and tumor tissues from patients undergoing treatment with MEDI4736+tremelimumab. In these comparisons, a paired t-test or Student t-tests will be performed. Because approximately 20 comparisons of immune cell populations will be performed, a Bonferroni correction will be applied to correct for multiple comparisons. For the comparison of overall survival and recurrence-free survival between treatment groups, log-rank test will be used. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients. SAS software will be used for all other statistical analyses.

Sample Size Determination:

The primary objective is comparison of the ratio of CD8/Treg before and after treatment with combination MEDI4736+Tremelimumab. A total of 20 evaluable subjects will be enrolled in this study for 24 months and 8 subjects will be assigned to combination MEDI4736+Tremelimumab (8 subjects to MEDI4736 only and 4 subjects to control). The outcome of interest in this study is a change in ratio of CD8/Treg before and after treatment with combination MEDI4736+Tremelimumab within subjects. Our sample size was therefore calculated based upon the change in CD8/Treg ratio in tumor tissues before and after treatment with combination MEDI4736+Tremelimumab therapy. This sample size calculation is also applicable to our secondary objectives including the change in CD8/Treg ratio in tumor tissues before and after treatment with MEDI4736 monotherapy.

Because there are no data available to estimate a change of ratio of CD8/Treg before and after the treatment in MPM, we utilized data from preclinical reports, and clinical data in melanoma patients. The ratio of CD8 T cells to regulatory T cells (CD8/Treg) is increased by the blockade of CTLA-4 and PD-1 within B16 mouse melanoma tumors (CD8/Treg ratio 2 in untreated, 11 in αCTLA-4 treated, and 8 in αPD-1 treated) (Curran et al., 2010), and this ratio is predictive of therapeutic efficacy in this model (Quezada et al., 2006). In a recent report of melanoma patients undergoing PD-1 blockade, subjects who had a significant clinical response were found to have an increase in the number of intratumoral CD8 T cells following drug delivery (15.1 ± 6.6 to 36.0 ± 8.4 CD8 T cells/mm^2) (Tumeh et al., 2014). Further, ourour pilot data from 6 subjects with MPM the log transformed ratio of CD8/Treg was approximately normally distributed with a mean of 1.94(6.96 in raw scale) and standard deviation of 0.808(2.24 in raw scale). Assuming that repeat values are moderately correlated(r=0.5), then the difference between before and after the combination treatment will also have a standard deviation of 0.808(2.24 in raw scale). We estimate that we will have 80% power (alpha=5%, a paired t-test) to detect an increased log ratio CD8/Treg of 2.87(17.71 in raw scale) after the combination treatment with 8 subjects.

SCHEDULE OF STUDY ASSESSMENTS

Schedule of study assessments: Screening and Treatment Period (24 months: maximum of 1 dose)

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)	**Screening** (Up to 28 days before or on Day 1)	**Baseline**	**Mediastinoscopy & Thoracoscopy**	**Oncology Visit**	**Infusion** (3 days-3 weeks after mediastinoscopy & thoracoscopy)	**Clinic Visit**	**Surgical Resection** 1-6 weeks after infusion[i]	**Follow-up** (after expected average 2 week hospital stay)
					All assessments to be performed pre-infusion unless stated otherwise			
Day	**-28 to 1**	**1**						
Week	**-4 to 1**	**0**	**0-1**	**0-3**	**0-3**	**1-6**	**1-6**	**After dis-charge from hospital** 1 week later, then 2 weeks later, then 4 weeks later. (±7 days)
Written informed consent/assignment of subject identification number	X							
Preliminary eligibility fulfillment (investigator's opinion)	X							
Demography and history of tobacco and alcohol use	X							
Previous treatments for malignant pleural mesothelioma	X							
Archival FFPE tumor tissue sample for PD-L1 assay, if applicable								

Schedule of study assessments: Screening and Treatment Period (24 months: maximum of 1 dose)

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)	**Screening** (Up to 28 days before or on Day 1)				**All assessments to be performed pre-infusion unless stated otherwise**			
		Baseline	**Mediastinoscopy & Thoracoscopy**	**Oncology Visit**	**Infusion** (3 days-3 weeks after mediastinoscopy & thoracoscopy)	**Clinic Visit**	**Surgical Resection** 1-6 weeks after infusion[i]	**Follow-up** (after expected average 2 week hospital stay)
Day	**-28 to 1**	**1**						
Week	**-4 to 1**	**0**	**0-1**	**0-3**	**0-3**	**1-6**	**1-6**	**After dis-charge from hospital** 1 week later, then 2 weeks later, then 4 weeks later. (±7 days)
Recent formalin-fixed tumor biopsy for PD-L1 assay, if applicable								
Formal verification of eligibility criteria			X[h]					
Medical and surgical history	X							
Hepatitis B and C; HIV	X							
Urine hCG or serum βhCG[a]	X				As clinically indicated			
MEDI4736 administration					X (or MEDI473 + tremelimumab)			
MEDI4736 + tremelimumab					X (or MEDI4736)			
Physical examination[b]	X	X				X		X
Vital signs (pre-during and post-infusion vital signs assessments)[c]	X	X			X			

Schedule of study assessments: Screening and Treatment Period (24 months: maximum of 1 dose)

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)	**Screening** (Up to 28 days before or on Day 1)	**Baseline**	**Mediastinoscopy & Thoracoscopy**	**Oncology Visit**	**Infusion** (3 days-3 weeks after mediastinoscopy & thoracoscopy)	**Clinic Visit**	**Surgical Resection** 1-6 weeks after infusion[i]	**Follow-up** (after expected average 2 week hospital stay)
					All assessments to be performed pre-infusion unless stated otherwise			
Day	**-28 to 1**	**1**						
Week	**-4 to 1**	**0**	**0-1**	**0-3**	**0-3**	**1-6**	**1-6**	**After dis-charge from hospital** 1 week later, then 2 weeks later, then 4 weeks later.
								(±7 days)
Weight	X	X				X		
Electrocardiogram[d]		X			X			X (week 16 only)
Adverse event/serious adverse event assessment	X	X				All visits		
Concomitant medications	X	X				All visits		
Palliative radiotherapy	As clinically indicated							
ECOG performance status	X	X				X		
Liver enzyme panel[f]					X			
Serum Chemistry (Complete clin chem. panel including Liver Enzymes, Amylase, Lipase)[e]	X	X				X		
Thyroid function tests (TSH and fT3 and fT4)[f]	X	X				X		

Schedule of study assessments: Screening and Treatment Period (24 months: maximum of 1 dose)

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)	**Screening** (Up to 28 days before or on Day 1)	**Baseline**	**Mediastinoscopy & Thoracoscopy**	**Oncology Visit**	**Infusion** (3 days-3 weeks after mediastinoscopy & thoracoscopy)	**Clinic Visit**	**Surgical Resection** 1-6 weeks after infusion[i]	**Follow-up** (after expected average 2 week hospital stay)
					All assessments to be performed pre-infusion unless stated otherwise			
Day	**-28 to 1**	**1**						
Week	**-4 to 1**	**0**	**0-1**	**0-3**	**0-3**	**1-6**	**1-6**	**After dis-charge from hospital** 1 week later, then 2 weeks later, then 4 weeks later. (±7 days)
Hematology[e]	X	X				X		
Urinalysis[g]	X					X		
Coagulation parameters[h]	X				As clinically indicted			
Tumor tissue collection for Cytof, IHC, gene analysis			X				X	
Blood collection for Cytof			X				X	
Oncology visit discuss treatment				X				
Clinic visit discuss surgery						X		

[a] Pre-menopausal female subjects of childbearing potential only
[b] Full physical examination at baseline; targeted physical examination at other timepoints
[c] Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated
  If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

[d] On Day 1 and as clinically indicated. ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion.
[e] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion.
[f] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
[g] Urinalysis performed at Screening, Day 1, and as clinically indicated.
[h] Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.
[i] Patients in control arm can proceed from mediastinoscopy and thoracoscopy directly to resectional surgery.
[j] This eligibility will be checked after the laparoscopy/mediastinoscopy procedure when the path report becomes available.

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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
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
B7 H1	B7 homolog 1
CD	cluster of differentiation
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
Cmax	peak concentration
Cmax,ss	peak concentration at steady state
Cmin	trough concentration
Cmin,ss	trough concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
CyTOF	time-of-flight mass cytometry
DC	disease control
DCR	disease control rate

Abbreviation or special term	Explanation
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
EPP	extrapleural pneumonectomy
Fc	fragment crystallizable
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
ICOS	inducible T-cell co-stimulator
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IHC	immunohistochemistry

Abbreviation or special term	Explanation
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody
MDSC	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MPM	malignant pleural mesothelioma
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
P/D	pleurectomy/decortication
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)

Abbreviation or special term	Explanation
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
t½	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
Tmax	time to peak concentration
Tmax,ss	time to peak concentration at steady state
TNF-α	tumor necrosis factor alpha

Abbreviation or special term	Explanation
Treg	regulatory T-cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
WFI	water for injection
WHO	World Health Organization
(w/v)	weight/volume

1. INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive malignancy of the pleura that is associated with prior exposure to asbestos and is fatal in most cases. The tumor most commonly arises within the parietal pleura and spreads locally to the ipsilateral visceral pleura, lung, chest wall, diaphragm, pericardium, and mediastinum. Treatment with standard cytotoxic chemotherapy regimens, including cisplatin and pemetrexed, results in an extension of the median survival time to 12 months, compared with cisplatin alone (Vogelzang et al, 2003). For patients with disease confined to the ipsilateral hemithorax, surgical resection combined with systemic or intracavitary chemotherapy, radiation therapy, and/or other local modalities, has been offered with reports of more optimistic outcomes. The operative procedures most commonly used in these multimodal approaches include the following: extrapleural pneumonectomy (EPP), which involves en bloc resection of the lung, pericardium, diaphragm, visceral, and parietal pleura; and pleurectomy/decortication (P/D), which involves resection of the visceral and parietal pleura with or without resection of the pericardium and/or diaphragm. Nonetheless, the majority of these patients will suffer from recurrence and ultimately succumb to the disease (Rusch et al., 2012; Sugarbaker et al., 2014). There is a clear need for better systemic therapies for MPM.

1.1 Disease Background

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing, which allows them to develop unchecked. One such mechanism involves the 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.

The blockade of negative regulatory signals to T-cells, such as PD-L1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4), has shown promising clinical activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and prevents the interaction of CTLA-4 with cluster of differentiation (CD) 80 and CD86, which results in enhanced T-cell activation and proliferation (Lipson et al., 2011). Ipilimumab was shown to extend survival in patients with

advanced melanoma (Hodi et al., 2010), and was granted United States Food and Drug Administration (FDA) approval in 2011 for the treatment of metastatic melanoma.

PD-L1 (B7 homolog 1 [B7 H1], CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T cells, B cells, dendritic cells (DC), macrophages, mesenchymal stem cells, bone marrow-derived mast cells, and in various non-hematopoietic cells (Keir et al., 2008). The normal function of PD-L1 is to regulate the balance between T-cell activation and tolerance through the interaction with two receptors, programmed death 1 (PD-1, CD279) and CD80 (B7-1). In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells, which delivers an inhibitory signal to those T cells, preventing them from killing target tumor cells and thus protecting the tumor from immune elimination (Zou et al., 2008). In the clinic, antibody-mediated blockade of PD-L1 induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of the disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers, including non-small-cell lung cancer, melanoma, and renal-cell cancer (Brahmer et al., 2012). Similarly, treatment with anti-PD-1 antibodies produced objective responses in approximately one in four to one in five patients with non-small-cell lung cancer, melanoma, or renal-cell cancer (Topalian et al., 2012).

Pre-clinical data and clinical research suggests that the concurrent targeting of immunologic checkpoints may generate superior anti-tumor activity when compared with a single-agent checkpoint blockade, which may translate into higher and more durable rates of response. Mouse data indicate that the mechanisms of activation of sites known to be involved in the activity of CTLA-4 and PD-1 are non-redundant, and therefore targeting both pathways may have additive or synergistic activity (Pardoll, 2012). For example, in mouse tumor models, the combination of PD-1 and CTLA-4 blockade achieved more pronounced anti-tumor activity than the blockade of either pathway alone (Curran et al., 2010; Duraiswamy et al., 2013). Notably, in models of murine melanoma, anti-PD-1 blockade increased the expression of CTLA-4 on intratumoral T cells, and reciprocally, CTLA-4 blockade increased PD-1 expression on intratumoral T cells, suggesting one potential mechanism for the increased efficacy of dual checkpoint therapy (Curran et al., 2010). The concurrent administration of monoclonal antibodies to CTLA-4 (ipilimumab) and PD-1 (nivolumab) was recently evaluated in a Phase I trial that showed impressive preliminary evidence of improved benefit in advanced melanoma patients. The overall response rate was 53% at the maximum tolerated dose. Three patients presented with a complete response (CR), and all responding patients experienced a ≥80% decline in tumor burden at 12 weeks (Wolchok et al., 2013).

MPM has recently been recognized as an immunogenic tumor, and durable clinical responses to immunotherapy have been obtained in the laboratory setting (Tan et al., 2014; Adusumilli

2014; Adusumilli et al., 2014; Fridlender et al., 2009; Anraku et al., 2008; Wu et al., 2012). In murine models of MPM, for example, CTLA-4 blockade results in significant anti-tumor responses (Wu et al., 2012). In the clinic, tremelimumab has shown encouraging clinical activity and an acceptable safety and tolerability profile in patients with advanced MPM who have been previously treated with cytotoxic chemotherapy (Calabro et al., 2013).

1.2 MEDI-4736 Background

Investigators should be familiar with the current MEDI4736 Investigator Brochure (IB).

MEDI4736 is being developed as a potential anticancer therapy for patients with advanced solid tumors. MEDI4736 is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.2.1 Summary of non-clinical experience

The non-clinical experience is fully described in the current version of the MEDI4736 Investigator's Brochure (IB).

MEDI4736 binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. *In vitro* studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, MEDI4736 demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that MEDI4736 inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of MEDI4736. Following intravenous (IV) administration, the PK of MEDI4736 in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life (t1/2) increased with increasing doses, suggesting saturable target binding-mediated clearance of MEDI4736. No apparent gender differences in PK profiles were observed for MEDI4736.

In general, treatment of cynomolgus monkeys with MEDI4736 was not associated with any MEDI4736-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:MEDI4736 immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to MEDI4736. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of MEDI4736.

Finally, data from the pivotal 3-month GLP toxicity study with MEDI4736 in cynomolgus monkeys showed that subchronic dosing of MEDI4736 was not associated with any adverse effects. Therefore, the NOAEL of MEDI4736 in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the *in vivo* toxicology data, no unexpected membrane binding of MEDI4736 to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

1.2.2 Summary of clinical experience

Clinical experience with MEDI4736 is fully described in the current version of the MEDI4736 Investigator's Brochure.

As of the DCO dates (15Apr2015 to 12Jul2015), a total of 1,883 subjects have been enrolled and treated in 30 ongoing MEDI4736 clinical studies, including 20 sponsored and 10

collaborative studies (Table 1.2-1). Of the 1,883 subjects, 1,279 received MEDI4736 monotherapy, 440 received MEDI4736 in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

Pharmacokinetics and Product Metabolism

The PK and immunogenicity profiles of MEDI4736 as monotherapy and combined with tremelimumab are described below based on data from key studies.

Pharmacokinetics and Immunogenicity Profile of MEDI4736 Monotherapy

Study CD-ON-MEDI4736-1108: As of 09Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 following treatment with MEDI4736 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 MEDI4736 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 MEDI4736 ≥ 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 MEDI4736 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.

Pharmacokinetics and Immunogenicity Profile of MEDI4736 Combination Therapy

Study D4190C00006: As of 20Feb2015, MEDI4736 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 MEDI4736 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 MEDI4736 and tremelimumab was observed over the dose range of 3 to 15 mg/kg MEDI4736 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 MEDI4736 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 MEDI4736 and 53 subjects for tremelimumab in Study D4190C00006. Four of 60 subjects were ADA positive for anti-MEDI4736 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 MEDI4736 or tremelimumab, and no obvious association between ADA and safety or efficacy. MEDI4736 has also been combined with other anticancer agents, including gefitinib, dabrafenib, and trametinib. To date, no PK interaction has been observed between MEDI4736 and these agents.

Safety

The safety profile of MEDI4736 as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs.
Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with MEDI4736 and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with MEDI4736 and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with MEDI4736 monotherapy and MEDI4736 and tremelimumab combination therapy in key clinical studies are described below.

Adverse Event Profile of MEDI4736 Monotherapy

Study CD-ON-MEDI4736-1108: The safety profile of MEDI4736 monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108 has been broadly consistent with that of the overall 1,279 subjects who have received MEDI4736 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 MEDI4736 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108, 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 MEDI4736 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 MEDI4736 were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of MEDI4736 monotherapy in Study CD-ON-MEDI4736-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) treated with MEDI4736 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 MEDI4736 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 MEDI4736. 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 MEDI4736. Twenty-three of 303

subjects= (7.6%) permanently discontinued MEDI4736 treatment due to AEs. Events that led to discontinuation of MEDI4736 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.

Adverse Event Profile of MEDI4736 and Tremelimumab Combination Therapy
Study D4190C00006: The safety profile of MEDI4736 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 MEDI4736 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 MEDI4736 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).

Efficacy

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 andD4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the 4 studies.

Study CD-ON-MEDI4736-1108: Overall, 456 of 694 subjects treated with MEDI4736 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in

bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

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

Study CD-ON-MEDI4736-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of MEDI4736 and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥ 12 weeks) was 79.4%.

Study D4190C00006: Of the 102 subjects with advanced NSCLC treated with MEDI4736 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.

1.3 Research hypothesis

Our hypothesis is that neoadjuvant therapy with anti-PD-L1 monoclonal antibody MEDI4736 in combination with anti-CTLA-4 monoclonal antibody tremelimumab will result in favorable alterations of the intratumoral immunologic environment in subjects undergoing resectional surgery for malignant pleural mesothelioma (MPM).

1.4 Rationale for conducting this study

Malignant pleural mesothelioma (MPM) is an aggressive malignancy of the pleura that is associated with prior exposure to asbestos and is fatal in most cases. The tumor most commonly arises within the parietal pleura and spreads locally to the ipsilateral visceral pleura, lung, chest wall, diaphragm, pericardium, and mediastinum. Treatment with standard cytotoxic chemotherapy regimens, including cisplatin and pemetrexed, results in an extension of the median survival time to 12 months, compared with cisplatin alone (Vogelzang, 2003). For patients with disease confined to the ipsilateral hemithorax, surgical resection combined with systemic or intracavitary chemotherapy, radiation therapy, and/or other local modalities, has been offered with reports of more optimistic outcomes. The operative procedures most commonly used in these multimodal approaches include the following: extrapleural pneumonectomy (EPP), which involves en bloc resection of the lung, pericardium, diaphragm, visceral, and parietal pleura; and pleurectomy/decortication (P/D), which involves resection of the visceral and parietal pleura with or without resection of the pericardium and/or diaphragm (Rice et al., 2011). Nonetheless, the majority of these patients will suffer from recurrence and ultimately succumb to the disease (Rusch et al., 2012; Sugarbaker et al., 2014). There is a clear need for better systemic therapies for MPM.

The blockade of negative regulatory signals to T-cells, such as PD-L1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4), has shown promising clinical activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and prevents the interaction of CTLA-4 with cluster of differentiation (CD) 80 and CD86, which results in enhanced T-cell activation and proliferation (Lipson et al., 2011). Ipilimumab was shown to extend survival in patients with advanced melanoma (Hodi et al., 2010), and was granted United States Food and Drug Administration (FDA) approval in 2011 for the treatment of metastatic melanoma.

PD-L1 (B7 homolog 1 [B7 H1], CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T cells, B cells, dendritic cells (DC), macrophages, mesenchymal stem cells, bone marrow-derived mast cells, and in various non-hematopoietic cells (Keir et al., 2008). The normal function of PD-L1 is to regulate the balance between T-cell activation and tolerance through the interaction with two receptors, programmed death 1 (PD-1, CD279) and CD80 (B7-1). In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells, which delivers an inhibitory signal to those T cells, preventing them from killing target tumor cells and thus protecting the tumor from immune elimination (Zou et al., 2008). In the clinic, antibody-mediated blockade of PD-L1 induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of the disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers, including non-small-cell lung cancer, melanoma, and renal-cell

cancer (Brahmer et al., 2012). Similarly, treatment with anti-PD-1 antibodies produced objective responses in approximately one in four to one in five patients with non-small-cell lung cancer, melanoma, or renal-cell cancer (Topalian et al., 2012).

Pre-clinical data and clinical research suggests that the concurrent targeting of immunologic checkpoints may generate superior anti-tumor activity when compared with a single-agent checkpoint blockade, which may translate into higher and more durable rates of response. Mouse data indicate that the mechanisms of activation of sites known to be involved in the activity of CTLA-4 and PD-1 are non-redundant, and therefore targeting both pathways may have additive or synergistic activity (Pardoll, 2012). For example, in mouse tumor models, the combination of PD-1 and CTLA-4 blockade achieved more pronounced anti-tumor activity than the blockade of either pathway alone (Curran et al., 2010; Duraiswamy et al., 2013). Notably, in models of murine melanoma, anti-PD-1 blockade increased the expression of CTLA-4 on intratumoral T cells, and reciprocally, CTLA-4 blockade increased PD-1 expression on intratumoral T cells, suggesting one potential mechanism for the increased efficacy of dual checkpoint therapy (Curran et al., 2010). The concurrent administration of monoclonal antibodies to CTLA-4 (ipilimumab) and PD-1 (nivolumab) was recently evaluated in a Phase I trial that showed impressive preliminary evidence of improved benefit in advanced melanoma patients. The overall response rate was 53% at the maximum tolerated dose. Three patients presented with a complete response (CR), and all responding patients experienced a ≥80% decline in tumor burden at 12 weeks (Wolchok et al., 2013).

MPM has recently been recognized as an immunogenic tumor, and durable clinical responses to immunotherapy have been obtained in the laboratory setting (Tan et al., 2014; Adusumilli 2014; Adusumilli et al., 2014; Fridlender et al., 2009; Anraku et al., 2008; Wu et al., 2012). In murine models of MPM, for example, CTLA-4 blockade results in significant anti-tumor responses (Wu et al., 2012). In the clinic, tremelimumab has shown encouraging clinical activity and an acceptable safety and tolerability profile in patients with advanced MPM who have been previously treated with cytotoxic chemotherapy (Calabro et al., 2013).

The effects of PD-L1 or CTLA-4 blockade on the tumor microenvironment in humans are largely unknown. At Baylor College of Medicine, we surgically treat 2-4 patients with MPM per week, and are therefore uniquely positioned to study this disease. This phase II, window of opportunity, neoadjuvant trial in patients with surgically resectable MPM will comprehensively characterize the influence of MEDI4736 and the combination therapy of MEDI4736 + tremelimumab on the local immunologic environment of the tumor, as well as the systemic blood and bone marrow compartments. Our primary objective will be a comparison of the CD8/Treg ratio, the percentage of ICOS+ CD4 T cells, and the tissue

expression of PD-1, PD-L1, and CTLA-4 before and after the delivery of the immunotherapeutic agent(s).

Our **hypothesis** is that neoadjuvant therapy with anti-PD-L1 monoclonal antibody MEDI4736 in combination with anti-CTLA-4 monoclonal antibody tremelimumab will result in favorable alterations of the intratumoral immunologic environment in subjects undergoing resectional surgery for malignant pleural mesothelioma (MPM). The **primary objective** of this study will be comparison of the ratio of intratumoral cytotoxic T cells to regulatory T cells (CD8/Treg) before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy. In vitro, an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of anti-tumor T-cells (Blank et al., 2006). The ratio of CD8 T cells to regulatory T cells (CD8/Treg) is increased by the blockade of CTLA-4, PD-1, or PD-L1 within B16 mouse melanoma tumors (Curran et al., 2010), and this ratio is predictive of therapeutic efficacy in this model (Quezada et al., 2006). Importantly, combination therapy with CTLA-4 and PD-1 increases the CD8/Treg ratio more significantly than monotherapy (Curran et al., 2010). In a recent report of melanoma patients undergoing PD-1 blockade, subjects who had a significant clinical response were found to have an increase in the number of intratumoral CD8 T cells following drug delivery (Tumeh et al., 2014), suggesting that PD-1 blockade favorably influences the tumor microenvironment. The levels of tumor-infiltrating CD8 T-cells have been correlated with improved prognosis in MPM (Anraku et al., 2008) and a number of other malignancies, including colorectal, melanoma, and lung cancer (Pagès et al., 2010), which further suggests that an intratumoral CD8 T-cell response is beneficial to patients.

Based on these findings, we expect that the addition of tremelimumab to MEDI4736 in patients with MPM will result in an increased percentage of intratumoral CD4 T cells that express ICOS. Treatment with anti-CTLA-4 antibodies in patients with melanoma or bladder cancer has resulted in a significant increase of blood ICOS+ CD4 T cells (Ng Tang et al., 2013; Liakou et al., 2008; Chen et al., 2009; Vonderheide et al., 2010). Notably, this statistically significant increase in ICOS+ CD4 blood T cells was seen after one dose of the drug (Ng Tang et al., 2013). In addition, it has been reported that a sustained increase in the frequency of ICOS+ CD4 T cells was correlated with a clinical benefit in patients with melanoma undergoing anti-CTLA-4 therapy (Carthon et al., 2010). Moreover, in patients undergoing radical cystectomy for bladder cancer who received 2 doses of the anti-CTLA-4 antibody ipilimumab, a significant increase in the percentage of ICOS+ CD4 T cells was seen in the tumor tissues (Liakou et al., 2008).

We additionally hypothesize that the addition of tremelimumab to MEDI4736 will increase the tumor expression of PD-L1, which provides a potential mechanism for the improved

efficacy of combination PD-L1 and CTLA-4 blockade compared with a single-agent therapy. PD-L1 is expressed with a relatively high frequency in a broad range of human malignancies, up to 88% in some cancers. In a number of these cancers, including lung (Mu et al., 2011), renal (Krambeck et al., 2007), pancreatic (Nomi et al., 2007), and ovarian cancer (Hamanishi et al., 2007), the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. PD-LI is expressed in a substantial proportion of MPM tumors (21% of epithelial MPM tumors and 74% of non-epithelial MPM tumors), and its expression is associated with a decreased overall survival (Mansfield et al., 2014). Although it appears that the selection of patients based on PD-L1 expression within the tumor microenvironment may improve the probability and/or quality of responses to PD-1 pathway -targeting agents, there remain a number of patients with PD-L1-negative tumors that respond to the blockade with the PD-LI inhibitor MEDI4736 (Brahmer et al., 2014). Furthermore, the expression of PD-L1 may not have as much of an impact when a combination of checkpoint inhibitors is utilized. For example, a study investigating the combination of a PD-1 inhibitor (nivolumab) and a CTLA-4 inhibitor (ipilimumab) in patients with melanoma suggested that the combination of CTLA-4 and PD-1 blockade may have an effect independent from tumoral PD-L1 expression (Wolchok et al., 2013). Interestingly, in mouse models of melanoma, PD-1 blockade increased the expression of CTLA-4 on intratumoral T cells, and reciprocally, CTLA-4 blockade increased PD-1 expression on intratumoral T cells. This finding may provide an explanation for the synergistic activities of these two drugs, and we expect to uncover similar findings in human MPM tumors after treating patients with these drugs.

1.5 Benefit/risk and ethical assessment

Benefits/risk associated with MEDI4736

Clinical activity has been observed across the 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006) for which partial efficacy data are available.

• **Study CD-ON-MEDI4736-1108:** Overall, 456 of 694 subjects treated with MEDI4736 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 subjects, the ORR, based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and DCR-24w ranged from 4.2% in 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, HCC (n = 3 each, 33.3% each), NSCLC (n = 86; 26.7%), and SCCHN (n = 22; 18.2%). In the PD-L1-positive subset, DCR-24w was

highest in advanced cutaneous melanoma (n = 3; 66.7%), NSCLC (n = 86; 36.0%), HCC and bladder cancer (n = 3 each; 33.3% each), and SCCHN (n = 22; 18.2%).

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

• **Study CD-ON-MEDI4736-1161:** Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of MEDI4736 and BRAFi/MEKi, 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The confirmed and unconfirmed DCR (CR + PR + SD) for ≥ 12 weeks was 79.4%.

• **Study D4190C00006:** Of the 102 subjects with advanced NSCLC treated with MEDI4736 in combination with tremelimumab, 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.

Benefit/risk associated with tremelimumab:

In the clinical development program of tremelimumab and that of the related anti-CTLA-4 mAb, ipilimumab, a pattern of efficacy has emerged that appears to be consistent across tumor types. Response rates are generally low (~10%); however, in those subjects who respond, the responses are generally durable, lasting several months even in subjects with aggressive tumors (e.g., refractory metastatic melanoma). In a large Phase 3 study of tremelimumab versus DTIC/temozolomide in subjects with advanced melanoma, the median OS was 12.6 months for tremelimumab versus 10.7 months for DTIC/temozolomide (HR = 1.1416, p = 0.1272).

The safety profile across the tremelimumab nonclinical and clinical programs is dominated by immune-mediated reactions that can result in an inflammatory response. The important potential risks for tremelimumab that require further evaluation in clinical studies are immune-mediated gastrointestinal events such as colitis, endocrinopathies, dermatitis, pancreatitis, hepatitis, pneumonitis, neurotoxicities, cytopenias, and nonimmune-mediated infusion-related reactions, anaphylaxis and serious allergic reactions. Adverse events similar to those reported with ipilimumab were observed during clinical development of tremelimumab in melanoma, with diarrhea (40%), pruritus (23%), rash (22%), nausea (22%), and fatigue (17%) being the most common (Kirkwood et al, 2010). Grade 3 or higher AEs

observed were diarrhea (11%), fatigue (2%), rash (1%), nausea (1%), vomiting (1%), and anorexia (1%).

Potential risks associated with tremelimumab include immune-mediated gastrointestinal events including colitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); immune-mediated dermatitis including urticaria, skin exfoliation, and dry skin; immune-mediated endocrinopathies including hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism; immune-mediated hepatitis including autoimmune hepatitis, and increased serum alanine aminotransferase and aspartate aminotransferase; immune-mediated pancreatitis including autoimmune pancreatitis, and lipase and amylase elevation; immune-mediated respiratory tract events including pneumonitis and interstitial lung disease; immune-mediated nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and myasthenia gravis (the latter reported with combination of tremelimumab and MEDI4736); immune-mediated cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and serious allergic reactions; and headache, fatigue, and pyrexia.

Benefits/risks associated with combination treatment:

A total of 18 subjects have been treated, with 3 subjects each receiving 1 mg/kg tremelimumab and 3 mg/kg MEDI4736 Q4W, 1 mg/kg tremelimumab and 10 mg/kg MEDI4736 Q4W, 1 mg/kg tremelimumab and 15 mg/kg MEDI4736 Q4W, 3 mg/kg tremelimumab and 10 mg/kg MEDI4736 Q4W, 3 mg/kg tremelimumab and 15 mg/kg MEDI4736 Q4W, and 10 mg/kg tremelimumab and 15 mg/kg MEDI4736 Q4W. Overall, subjects have received between 0 and 7 doses of investigational products.

Across all dose cohorts, 17 of 18 subjects (94.4%) reported at least 1 AE (regardless of causality). The most frequently reported (> 3 subjects) AEs (all grades) were fatigue, pruritus, increased amylase, and arthralgia. Treatment-related AEs were reported in 13 of 18 subjects (72.2%). Of the 13 subjects, 4 had Grade 1, 3 had Grade 2, and 6 had ≥ Grade 3 events as maximum severity. Treatment-related Grade 3 events that occurred in 2 or more subjects were fatigue (6 subjects), increased amylase (4 subjects); diarrhea, nausea, and increased alanine aminotransferase (3 subjects each); and abdominal pain, colitis, epigastric discomfort, vomiting, increased aspartate aminotransferase, decreased appetite, and arthralgia (2 subjects each). No consistent pattern in the nature, dose-relationship, frequency, or severity of AEs has been noted with escalating doses of the combination.

Nine subjects have reported 15 SAEs (Table 5.3.1.6-2). None of the preferred terms were reported in more than 1 subject. The majority of the SAEs were Grade 3 or higher in severity. Half of the SAEs were considered related to investigational products. Three subjects with SAEs of disease progression, colitis, and malignant neoplasm progression, respectively, permanently discontinued investigational products due to these events. The event of malignant neoplasm progression, considered not related to investigational products, resulted in death. In

addition, 1 subject died due to the SAE of polymyositis that was considered related to both MEDI4736 and tremelimumab.

Benefits/risks associated with the study procedures

Both MEDI4736 and tremelimumab are administered intravenously. Possible risks associated with IV administration of the study drug(s) are infection, redness, swelling, and pain at the administration site.

2. STUDY OBJECTIVES

The objective of this study is to determine whether MEDI4736 or combination therapy with MEDI4736 + tremelimumab are associated with favorable alterations of the intratumoral immunologic environment in subjects undergoing resectional surgery for MPM.

2.1 Primary objective(s)

The primary objective of this study will be comparison of the ratio of intratumoral cytotoxic T cells to regulatory T cells (CD8/Treg) before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy.

2.2 Secondary objective(s)

The secondary objectives of this study are:

1) Comparison of the percentage of inducible T-cell co-stimulator (ICOS) positive intratumoral CD4 T cells before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy.
2) Comparison of tumor tissue expression (Ventana assay) of programmed death-ligand 1 (PD-L1) before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy.
3) Comparison of the ratio of the intratumoral CD8/Treg ratio in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone , and separately compare to untreated patients.
4) Comparison of the percentage of inducible T-cell co-stimulator (ICOS) positive intratumoral CD4 T cells in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone, and separately compare to untreated patients.

5) Comparison of tumor tissue expression (Ventana assay) of programmed death-ligand 1 (PD-L1) in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone, and separately compare to untreated patients. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.
6) Comparison of overall survival in patients treated with either MEDI-4736 alone or MEDI-4736 plus Tremelimumab with historical untreated controls. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.
7) Comparison of recurrence-free survival in patients treated with either MEDI-4736 alone or MEDI-4736 plus Tremelimumab with historical untreated controls. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.

3. STUDY DESIGN

3.1 Overview of study design

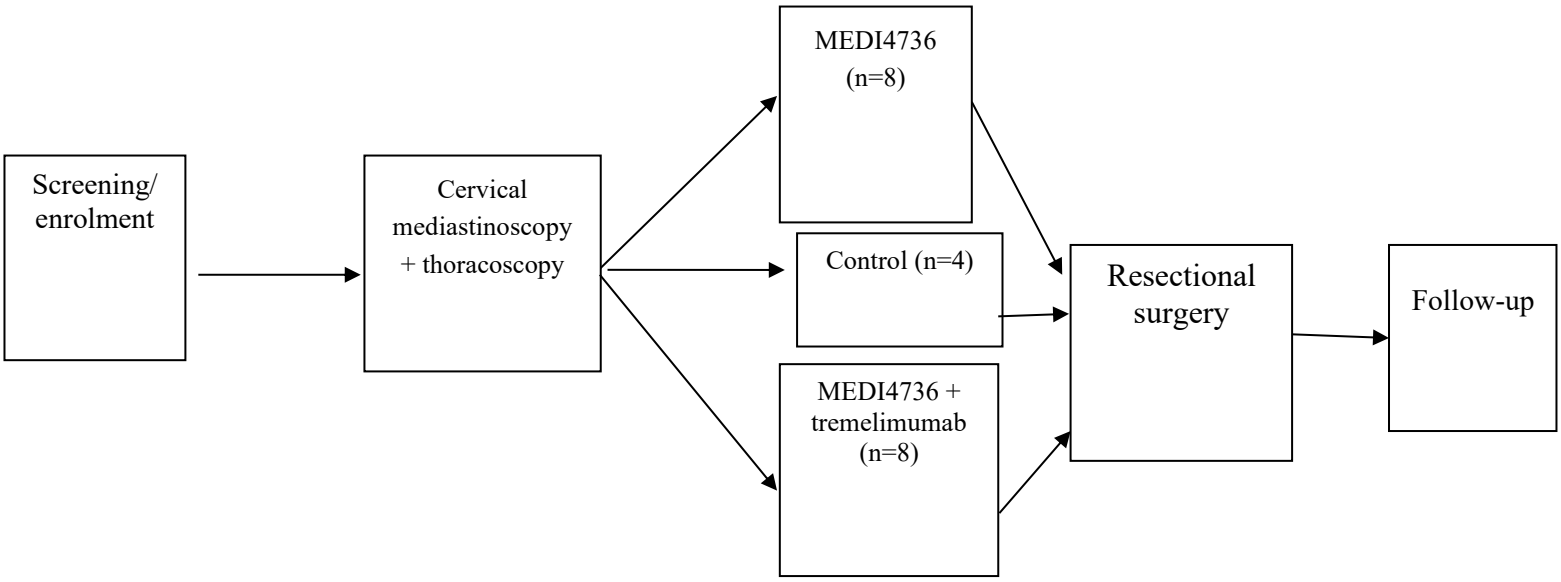
Subjects with MPM will undergo surgical mediastinal lymph node biopsy (cervical mediastinoscopy) and simultaneous surgical biopsy of the pleural tumor by thoracoscopy, at which time tumor tissue (at least 2 g) and peripheral blood will be collected for the study. These procedures are performed as our standard of care in the treatment of these subjects. The subject will be randomized. Three days to three weeks after the biopsy, 20 evaluable subjects (if tissue obtained) will be randomly treated with either MEDI-4736 alone (15 mg/kg once intravenously) (n=8) or MEDI-4736 (1500 mg once intravenously) plus tremelimumab (75 mg once intravenously) (n=8), or a control group (n=4) in a randomized controlled study design. There will be two treatment arms (MEDI4736 only and combination MEDI4736+tremelimumab) and one untreated arm (control). Randomization, stratified by receiving previous chemotherapy or not, will be performed and will help to minimize patient selection biases between three arms. Subjects under 30 kg will be treated with weight-based dosing for both MEDI4736 and Tremelimumab combination therapy. These patients are excluded from fixed based dosing to limit endotoxin exposure from the drug preparations. One to six weeks after the infusion, subjects will undergo resectional surgery, including extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D), at which time the tumor will be removed (typically 200-1000 g) and obtained for study. Four patients that do not undergo treatment with MEDI-4736 or tremelimumab will be included as controls. Blood will be obtained after the induction of general anesthesia for both the thoracoscopy procedure and the EPP or P/D resectional procedure, as is routinely done in these procedures. The sixth rib will be obtained at the time of the resection.

After the removal of the tumor, our standard protocol includes intraoperative heated chemotherapy using a lavage of intracavitary cisplatin in the presence of conserved renal function (Sugarbaker et al., 2013, 2014; Richards et al., 2006).

Tumor tissues obtained either by thorasoscopic biopsy or by resectional surgery will be evaluated by time-of-flight mass spectrometry (CyTOF) to determine intratumoral CD8/Treg ratios and percentage of ICOS positive CD4 T cells, and by immunohistochemistry (Ventana assay) to determine the tissue expression of PD-L1. These variables will be compared before and after treatment (changes within the same patient tumor), or between treatment groups (MEDI-4736 alone, MEDI-4736+tremelimumab, untreated) following treatment. Additional hypothesis-generating analyses will include a comprehensive systems based evaluation of the intratumoral immune cell population composition and phenotype phenotype [e.g., dendritic cells, macrophages, myeloid derived suppressor cells (MDSC), neutrophils, T-cell subsets, natural killer (NK) cells, and B cells], and immune-related gene expression using the nanostring system within the tumors, blood, and bone marrow of patients in all treatment groups.

3.2 Study schema

Figure 1 Study flow chart



Study Oversight for Safety Evaluation

There are no stopping criteria for this study except for the following:
a. Investigators decide to stop recruitment;
b. Sponsor decides to discontinue the study;
c. Subject withdraws consent at any time, for any reason.

Treatment may be put on hold, and pending full review of the data, the study may be stopped if any of the following criteria are met, and no further dosing or dose decisions will be taken pending a full safety review:
a. 1 study drug-related serious adverse event is reported
b. At least 4 subjects experience a similar unanticipated adverse event that is assessed

4. AS EITHER MODERATE OR SEVERE IN INTENSITY AND IS POTENTIALLY RELATED TO THE STUDY DRUG. SUBJECT SELECTION

Potential subjects will be evaluated from our clinical population of patients with MPM who are eligible for surgical resection and meet all inclusion/exclusion criteria. Study investigators will determine eligibility from clinical chemistry, hematology, physical examination, and a review of medical history during screening prior to enrollment in the study.

4.1 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

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

2. Age $\geq$ 18 years at time of study entry

3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

4. Adequate normal organ and marrow function as defined below:

   - 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 ≤ 1.5 x institutional upper limit of normal (ULN).
- 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>50 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:

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

5. Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
6. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
7. Surgically resectable MPM with no disease extension beyond the ipsilateral hemithorax
8. Planned resectional surgery for MPM [extrapleural pneumonectomy (EPP) or pleurectomy and decortication (P/D)]
9. Any MPM histology (epithelial, mixed, sarcomatoid)

   a. N0 or N1 nodal disease as present on preoperative chest CT and/or PET-CT

   b. N2 nodule disease if no progression after 2 cycles of standard chemotherapy. Progression will be considered if additional N1 or N2 disease develop during chemotherapy.

4.2 Exclusion criteria

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

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

2. Participation in another clinical study with an investigational product during the last 3 months

3. Any previous treatment with a PD1 or PD-L1 inhibitor, including MEDI4736

4. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 30 days prior to the first dose of study drug 30 days prior to the first dose of study drug for subjects who have received prior TKIs [e.g., erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C).

5. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid

6. Any unresolved toxicity (>CTCAE grade 2) from previous anti-cancer therapy.

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

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

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

10. History of primary immunodeficiency

11. History of allogeneic organ transplant

12. History of hypersensitivity to MEDI4736 or any excipient

13. History of hypersensitivity to tremelimumab or the combination of MEDI4736 + tremelimumab

14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent

15. Known history of previous clinical diagnosis of tuberculosis

16. History of leptomeningeal carcinomatosis

17. Receipt of live attenuated vaccination within 30 days prior to study entry or within 6 months of receiving MEDI4736 or MEDI + tremelimumab

18. Receipt of drugs with laxative properties and herbal or natural remedies for constipation within 90 days of receiving MEDI4736 or MEDI + tremelimumab

19. Receipt of sunitinib within 3 months of receiving tremelimumab

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

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

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

23. Subjects with uncontrolled seizures.

24. N3 nodal disease
25. History of interstitial lung disease/pneumonitis
26. No tissue is obtainable at thoracoscopy
27. Intraabdominal malignancy discovered at laparoscopy and proven pathologically, or nodal disease discovered at mediastinoscopy (N2 or N3 disease) and proven pathologically

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of MEDI4736 and/or tremelimumab

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

1. Withdrawal of consent or lost to follow-up
2. 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
3. Pregnancy or intent to become pregnant
4. Any AE that meets criteria for discontinuation as defined in Section 6.6
5. Adverse event related to tremelimumab, with the exception of toxicities that do not meet the criteria for discontinuation as defined in Section 6.6
6. Grade ≥ 3 infusion reaction
7. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
8. Initiation of alternative anticancer therapy including another investigational agent
9. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with MEDI4736

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

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.3.1 and Appendix B, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Withdrawal of consent

Patients are free to withdraw their consent to further participation in this trial without prejudice. If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

4.4 Replacement of subjects

We plan to replace subjects who are withdrawn from the study. The subject who replaces the withdrawn subject will receive the treatment (i.e., MEDI4736 only or MEDI4736 + tremelimumab) that was originally intended for the withdrawn subject.

5. INVESTIGATIONAL PRODUCT(S)

5.1 MEDI4736

The Investigational Products Supply section of AstraZeneca/MedImmune will supply MEDI4736 to the investigator as a concentrate for solution for infusion.

5.1.1 Formulation/packaging/storage

MEDI4736 is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0.

The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap over seal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial). The solution will be diluted with 0.9% (w/v) saline for IV infusion.

Unopened vials of liquid MEDI4736 must be stored at 2°C to 8°C (36°F to 46°F). MEDI4736 must be used within the individually assigned expiry date on the label.

In use storage and stability

Total in-use storage time from needle puncture of MEDI4736 vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). 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. MEDI4736 does not contain preservatives and any unused portion must be discarded.

5.1.2 Doses and treatment regimens

Subjects will be administered a 15 mg/kg intravenous dose of MEDI4736 once during the study.

5.1.3 Study drug preparation

Calculate the dose volume of MEDI4736 and number of vials needed for the subject to achieve the accurate dose according to Appendix A.

Preparation of infusion bags

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not** be prepared on the ward.

An additional volume of 0.9% (w/v) saline equal to the calculated volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to addition of MEDI4736.

The calculated volume of MEDI4736 is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Vials should be used for specific subjects and should not be shared between subjects.

5.1.4 Dose administration

MEDI4736 will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral vein.

Following preparation of MEDI4736, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter.

The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection), is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered.

5.1.5 Monitoring of dose administration

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment (see Section 6.2)

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued.

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

5.1.6 Accountability and dispensation

The investigator will assure that drug accountability records will maintain a current disposition of all investigational drugs, including their inventory and dispensing. Our records will comply with applicable regulations and guidelines that include:

1. Amount received and placed in storage;
2. Label ID number or batch number;
3. Amount dispensed, including unique subject identifiers;
4. Amount, if applicable, transferred from one area to another for dispensing or storage;
5. Non-study disposition (i.e., lost or unused);
6. Amount destroyed, if applicable;
7. Dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Responsibility Form.

5.1.7 Disposition of unused investigational study drug. At the completion of the study, all unused MEDI4736 will be returned to the sponsor

5.2 Tremelimumab

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

5.2.1 Formulation/packaging/storage

Tremelimumab Drug Product is formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, 0.27 mM disodium edetate dihydrate (EDTA), pH 5.5.

The Drug Product is supplied as a sterile IV solution in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL of tremelimumab with a nominal fill of 20 mL (accounting to 400 mg/vial). Vials containing tremelimumab must be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab is administered as an IV infusion after dilution in sterile, normal saline for injection. The product should be protected from light when not in use.

5.2.2 Doses and treatment regimens

Subjects will be administered MEDI4736 (1500 mg intravenously) + tremelimumab (75 mg intravenously) once during the study.

Subjects under 30 kg will be treated with weight-based dosing for both MEDI4736 and Tremelimumab combination therapy. These patients are excluded from fixed based dosing to limit endotoxin exposure from the drug preparations.

5.2.3 Product preparation

MEDI4736 + tremelimumab will be prepared following the procedures outlined in Section 5.1.3.

5.2.4 Dose administration

MEDI4736 + tremelimumab will be administered following the procedures outlined in Section 5.1.3.

5.2.5 Monitoring of dose administration

Subjects receiving MEDI4736 + tremelimumab will be monitored during and after the infusion following the procedures outlined in Section 5.2.5.

5.2.6 Accountability and dispensation

Drug accountability records will be kept as described in Section 5.1.6.

5.2.7 Disposition of unused investigational study drug

At the completion of the study, all unused MEDI4736 and Tremelimumab will be destroyed at the study site with proper documentation.

TREATMENT PLAN

5.3 Subject enrollment and randomization

We expect to enroll a total of 20 evaluable subjects (if tissue obtained at time of thoracoscopy and time of surgical resection) with surgically resectable MPM to this study over a period of 24 months. Subjects will be randomized. Subjects will be assigned to one of the three treatments (n = 8 MEDI4736, n = 8 MEDI4736 + tremelimumab, and n=4 control). All subjects will undergo surgical resection one to six weeks after the infusion.

5.3.1 Procedures for randomization

After mediastinoscopy + thoracoscopy, eligible subjects with MPM will be randomized in 2:2:1 ratio to one of three arms: MEDI4736 alone, MEDI4736 + tremelimumab, and a control group of neither MEDI4736 nor tremelimumab. A computer-generated randomization scheme may be generated by the Biostatistics Core, Baylor College of Medicine. Randomization will be accomplished via access to a secure website developed by the Biostatistics Core and automatically notified to the study coordinator or the investigator via email. Randomization will be stratified by receiving previous chemotherapy or not.

5.3.2 Procedures for handling subjects incorrectly enrolled or randomized

Subjects who are incorrectly enrolled in the study but have not yet received treatment with MEDI4736 or MEDI4736 + tremelimumab will be withdrawn from the study and will receive standard of care treatment for their MPM.

Subjects who are found to have been incorrectly enrolled after receiving treatment will be withdrawn from the study and will receive standard of care treatment for their MPM. Such patients will be replaced by eligible subjects with MPM. These subjects also will be followed for 90 days to track any AEs, SAEs, etc. from the treatment. These subjects will not be included in any data analyses.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This is an open-label study design; both investigators and subjects will know which study drug the subject is receiving.

5.4.2 Methods for unblinding the study

Not applicable.

5.5 Dosage and Administration

MEDI4736 (15 mg/kg intravenously) or MEDI4736 (1500 mg intravenously) + tremelimumab (75 mg intravenously) will be administered once during the study.

Subjects under 30 kg will be treated with weight-based dosing for both MEDI4736 and Tremelimumab combination therapy. These patients are excluded from fixed based dosing to limit endotoxin exposure from the drug preparations.

5.6 Dose Escalation Decision Rules

There will be no dose escalation in this study. Subjects randomized to either the MEDI4736 or MEDI4736 + tremelimumab will receive a single monotherapy or combination dose.

5.7 Definition of DLT

Dose-limiting toxicities (DLTs) will not be evaluated during this study.

5.8 Toxicity Management

5.8.1 MEDI4736

For adverse events (AEs) that are considered at least partly due to administration of MEDI4736 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 MEDI4736 along with appropriate continuing supportive care.

In addition, there are certain circumstances in which MEDI4736 should be permanently discontinued.

Based on the mechanism of action of MEDI4736 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.

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.

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) 1 November 2017 Version

General Considerations

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.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – 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. – Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 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 (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type

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) 1 November 2017 Version

General Considerations

Dose Modifications		Toxicity Management
Grade 3	Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., 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.
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.		
Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper		
Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).		

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Pediatric Considerations

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

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (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 (e.g., 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 methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such

		as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., 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 (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Diarrhea/Colitis	**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 (e.g., 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 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 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[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis:	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – 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 methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-

	life-threatening consequences, urgent intervention indicated)		PJP 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. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤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 >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤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 (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing 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 or IV equivalent, consider additional work up 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 (i.e., 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-PJP 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 >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×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 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	**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 (i.e., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

		alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator	

or elevated at baseline)	assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to 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 or IV equivalent, consider additional workup and 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, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• 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 Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate 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 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR):			

- **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise**
- **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise**
- **Grade 3-4: Permanently discontinue study drug/study regimen**

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 (e.g., 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 (e.g., 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 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	**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.

	baseline, then resume study drug/study regimen after completion of steroid taper.	– 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-PJP 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.
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-PJP 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 (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., 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. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids 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	**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].

		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.	– 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody

		testing.
Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). − If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study	**For Grade 2 (including those with symptomatic endocrinopathy):** − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. − For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). − Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen

	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.	interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP 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 and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of

		3. Doses of prednisone are ≤10 mg/day or equivalent.	endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
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 (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., 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	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin 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 immunosuppressive therapy (e.g., IV IG).

		event improves to Grade ≤1 and after completion of steroid taper.	
	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 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing 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 (e.g., 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 (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low

		threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, 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:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
Grade 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:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a

			monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or 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.
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 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing 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

		For Grade 4: Permanently discontinue study drug/study regimen.	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.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be

		obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion;	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks).

	intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.		Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**		**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician.

		– Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant

			– If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label

		for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
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; imAE immune-mediated 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; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); 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 (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard 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 (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

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 (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	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.

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."

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

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

6.1 Restrictions during the study

Contraception

Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 5) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of mono-therapy MEDI4736 or for 180 days after last dose of combination therapy with MEDI4736 and tremelimumab. The male partner of a female subject must also 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 is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding and egg cell donation throughout this period.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).

- Effective methods (including highly effective methods) of contraception are described in Table 5. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that not all methods in Table 1 are considered highly effective.

- Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use male condom plus spermicide (see Table 5) from screening through 90 days after the last dose of mono-therapy MEDI4736 or for 180 days after last dose of combination therapy with MEDI4736 and tremelimumab. 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 a male subject must use an effective method of contraception throughout this period.

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Table 5 Effective Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Male or female condom with or without spermicide[a,b,c] • Female cap, diaphragm or sponge with spermicide[a,b,c] • Copper T intrauterine device[e] • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[d,e]	• Implants[e] • Hormone shot or injection[e] • Combined pill[e] • Minipill[b] • Patch[e]

[a] Female partners of male subjects must use an effective method of birth control

[b] Not highly effective (i.e. failure rate of >1% per year)

[c] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

[d] This is also considered a hormonal method

[e] Highly effective (i.e. failure rate of <1% per year)

Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of MEDI4736 or tremelimumab.

6.2 Concomitant treatment(s)

6.2.1 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.

6.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than MEDI4736.

2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment, other than tremelimumab and surgical resection. Concurrent use of hormones for noncancerous-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is

acceptable. Local treatment of isolated lesions for palliative intent also is acceptable (e.g., by local surgery or radiotherapy).

3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).

4. Live attenuated vaccines within 30 days of MEDI4736 or tremelimumab dosing (i.e., 30 days prior to the first dose, during treatment with MEDI4736 and for 30 days post discontinuation of MEDI4736). Inactivated viruses, are permitted.

7. STUDY PROCEDURES

Subjects with MPM who are eligible for the study will be enrolled. Subjects first will undergo surgical mediastinal lymph node biopsy (cervical mediastinoscopy) and simultaneous surgical biopsy of the pleural tumor by thoracoscopy, at which time tumor tissue (goal of 2 g, which is generally available) and 25 ml of peripheral blood will be collected. These procedures are performed as our standard of care in the treatment of subjects with MPM. Three days to three weeks later subjects will receive either MEDI4736 (15 mg/kg once intravenously) or MEDI4736 (1500 mg once intravenously) + tremelimumab (75 mg once intravenously). Subjects under 30 kg will be treated with weight-based dosing for both MEDI4736 and Tremelimumab combination therapy. These patients are excluded from fixed based dosing to limit endotoxin exposure from the drug preparations. A control group will include patients who are not treated with MEDI4736 or Tremelimumab. One to six weeks after treatment, subjects will undergo resectional surgery including extrapleural pneumonectomy or pleurectomy/decortication at which time the tumor will be removed (typically 200-1000g) and obtained for study. Blood (25ml) also will be obtained for study. In addition, the sixth rib will be extracted at the time of the resectional procedure, as is routinely done during these procedures. After the removal of the tumor, our standard protocol (in the presence of conserved renal function) includes intraoperative heated chemotherapy using a lavage of

intracavitary cisplatin (Sugarbaker et al, 2013, 2014; Richards et al., 2006). Subjects will be followed for at least 90 days following the administration of the study drug for potential AEs or SAEs related to the study drug. Subjects will be followed for a longer period of time as standard of care.

7.1 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.

7.1.1 Screening Phase

Screening procedures will be performed up to 28 days before or on 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.

All subjects who screen for this study will have a clinical diagnosis of MPM (based upon CT, and/or PET-CT, and or MRI radiographic findings) but not all subjects will have had this diagnosis confirmed by a tissue biopsy. In either case patients undergo thoracoscopy to assess resectability of disease, and to obtain tissue or additional tissue, when necessary, for diagnosis. Thoracoscopy will be performed in these subjects after signing the ICF.

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 and height
- Review of prior/concomitant medications

- Imaging by CT/MRI, if applicable to study
- Clinical laboratory tests for:
    - Hematology (see Table 6)
    - Clinical chemistry (see Table 7)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies
    - Urinalysis (see Table 8)
    - Disease-specific tumor markers

7.1.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments.

Following the Screening Phase, subjects with MPM who are enrolled in the study will undergo surgical mediastinal lymph node biopsy (cervical mediastinoscopy) to evaluate nodal status and simultaneous surgical biopsy of the pleural tumor by thoracoscopy under general anesthesia, at which time tumor tissue (at least 2 g) and peripheral blood (25ml) will be collected for the study. These procedures are performed as our standard of care in the treatment of these subjects. The thoracoscopy procedure is part of our standard of care in both in subjects who have had a previous tissue biopsy and those who have not had a previous biopsy. It is performed to determine resectability of the tumor and to obtain tissue to confirm tissue diagnosis. In subjects who are consented to the study who have a suspected (clinical) diagnosis of MPM but not a tissue diagnosis, if the thoracoscopy procedure reveals that the subject does not have MPM, then these subjects will be removed from the study and their tissue and blood samples will be destroyed. These subjects will be replaced in the study.

Three days to three weeks later subjects will be treated with either MEDI4736 (15 mg/kg once intravenously) or MEDI4736 (1500 mg once intravenously) + tremelimumab (75 mg once intravenously). Subjects under 30 kg will be treated with weight-based dosing for both MEDI4736 and Tremelimumab combination therapy. These patients are excluded from fixed based dosing to limit endotoxin exposure from the drug preparations. A control group will include patients who are not treated with MEDI4736 or Tremelimumab. One to six weeks after treatment, subjects will undergo resectional surgery including extrapleural pneumonectomy or pleurectomy/decortication under general anesthesia, at which time the

tumor will be removed (typically 200-1000g) and obtained for study. Blood (25ml) also will be obtained for the study. The sixth rib will be obtained at the time of the resectional procedure as part of the routine procedure. After the removal of the tumor, our standard protocol (in the presence of conserved renal function) includes intraoperative heated chemotherapy using a lavage of intracavitary cisplatin.

7.1.3 End of Treatment

Subjects will be followed for a minimum of 12 months following entry into the study. As per standard of care, the great majority of patients will receive care with our group for the rest of their life, enabling measurement of disease free and overall survival, in our secondary objectives.

In general, subjects will spend approximately 8-14 days in the hospital following resection. After discharge from the hospital, subjects will return for follow-up visits at 1 week, 2 weeks, and 4 weeks and then every 4 months until death. Chest CT scans will be obtained every 4 months starting at the first 4-month visit.

Assessments for subjects who have completed MEDI4736 or MEDI4736 + tremelimumab but did not have resection are provided in APPENDIX B.

7.2 Description of study procedures

7.2.1 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.

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

ECGs are required at baseline, prior to the injection of study drug (MEDI4736 or MEDI4736 + tremelimumab) and at the end of treatment as well as at any other time point when clinically indicated.

ECGs recorded at baseline will be obtained in triplicate (all 3 within a 5-minute time period at least 1 minute apart); ECGs recorded during the treatment phase will be single tracing. All 12-lead ECGs should be recorded while the subject is in the supine position. A 12-lead ECG will be recorded for all subjects on study days noted in Section 8.1. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. On the infusion day, ECGs will be recorded within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. On the treatment day, vital signs will be measured within an hour prior to the start of infusion, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated.

7.2.2 Clinical laboratory tests

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

- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
    - Urine human chorionic gonadotropin
    - Serum beta-human chorionic gonadotropin (at screening only)
- Thyroid Stimulating Hormone

- free T3 and free T4 only if TSH is abnormal

- Other laboratory tests
  - Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
  - HIV antibody

Table 6 Hematology Laboratory Tests

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

Table 7 Clinical chemistry (serum or plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	
Alanine aminotransferase	Lipase
Amylase	
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 8 Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Color and appearance

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

7.3 Biological sampling procedures

Biological samples will be collected at two primary time points during the study. Tumor tissue (generally, at least 2 grams) and peripheral blood (25ml) will be collected during pre-treatment surgical mediastinal lymph node biopsy (cervical mediastinoscopy) and simultaneous surgical biopsy of the pleural tumor by thoracoscopy. One to six weeks after treatment, subjects will undergo resectional surgery, including extrapleural pneumonectomy or pleurectomy/decortication, at which time the tumor will be removed (typically 200-1000g) and blood (25ml) will be collected for the study.

7.3.1 Biomarker/Pharmacodynamic sampling and evaluation methods

Tissue biomarker immune response to MEDI4736 or MEDI4736 + tremelimumab will be determined on tissue and blood collected before and after the administration of the study drug(s), or in patients not receiving study drugs. The tissue biomarker immune responses that will be evaluated in this study include CD8/Treg ratios, percentage of ICOS+ CD4 T cells, and immune cell expression of PD-L1. CD8/Treg rations and percentage of ICOS+ CD4 T cells will be compared with CyTOF (time-of-flight mass cytometry) and/or flow cytometry. Tumor PD-L1 expression will be determined by immunohistochemistry. CyTOF and/or flow cytometry will be used to compare PD-L1 expression on specific immune cell and non-immune cell populations.

Bone marrow biomarker immune response will also be assessed. Bone marrow will be collected from a routinely resected sixth rib during the surgical resection scheduled post-treatment with MEDI4736 or MEDI4736 + tremelimumab, or in patients not receiving study drugs. A comprehensive evaluation of immune cell composition and phenotype with CyTOF will be conducted on bone marrow tissue as well as tumor tissue and peripheral blood. Appendix C details the complete CyTOF panel that will be used for each individual specimen.

7.3.2 Estimate of volume of blood to be collected

Blood samples will be drawn at two points: during the thoracoscopy procedure and during the resection procedure (P/D or EPP). In both cases, the sample will be drawn immediately after the induction of general anesthesia via a radial arterial catheter that is routinely placed for these procedures. A total of 50 cc will be drawn in the study (25-cc per time point).

7.3.3 Fresh tumor biopsies

Fresh tumor biopsies will be sampled from patients at two time points during the study. Prior to treatment with the study drug(s), patients will undergo surgical mediastinal lymph node biopsy (cervical mediastinoscopy) and simultaneous surgical biopsy of the pleural tumor by thoracoscopy under general anesthesia, at which time tumor tissue (generally 2 g) will be collected. One to six weeks after study drug(s) infusion, patients will undergo resectional surgery including extrapleural pneumonectomy or pleurectomy/decortication under general anesthesia, at which time the tumor will be removed (typically 200-1000 g) and obtained for study. These biopsied tissues will be used to determine tissue biomarker immune response to MEDI4736 or MEDI4736 + tremelimumab using CyTOF as described in Section 9.1.1 and 9.1.2.

7.3.4 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.

8. DISEASE EVALUATION AND METHODS

8.1.1 Primary Efficacy Variables

1) The primary objective of this study will be comparison of the ratio of intratumoral cytotoxic T cells to regulatory T cells (CD8/Treg) before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy. CD8/Treg ratios will be determined with CyTOF

8.1.2 Secondary Efficacy Variables

The secondary objectives of this study are:

1) Comparison of the percentage of inducible T-cell co-stimulator (ICOS) positive intratumoral CD4 T cells before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy. These data will be obtained using CyTOF

2) Comparison of tumor tissue expression (Ventana assay) of programmed death-ligand 1 (PD-L1) before and after treatment with combination MEDI-4736 and Tremelimumab checkpoint inhibitor therapy. These data will be obtained with IHC.

3) Comparison of the ratio of the intratumoral CD8/Treg ratio in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone , and separately compare to untreated patients. These data will be obtained with CyTOF.

4) Comparison of the percentage of inducible T-cell co-stimulator (ICOS) positive intratumoral CD4 T cells in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone, and separately compare to untreated patients. These data will be obtained with CyTOF.

5) Comparison of tumor tissue expression (Ventana assay) of programmed death-ligand 1 (PD-L1) in patients treated with combination therapy (MEDI-4736 and Tremelimumab) compared to either patients treated with MEDI-4736 alone, and separately compare to untreated patients. These data will be obtained with IHC.

6) Comparison of overall survival in patients treated with either MEDI-4736 alone or MEDI-4736 plus Tremelimumab with historical untreated controls. These data will be obtained from our standard of care follow up of these patients. Given the survival estimates of these patients from historical controls, these data can be evaluated approximately 2 year after surgery. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.

7) Comparison of recurrence-free survival in patients treated with either MEDI-4736 alone or MEDI-4736 plus Tremelimumab with historical untreated controls. Given the recurrence free survival estimates of these patients from historical controls, these data can be evaluated approximately 2 year after surgery. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients.

8) Additional tissue biomarker immune response to MEDI4736 or MEDI4736 + tremelimumab determined with CyTOF. A comprehensive evaluation of immune cell composition and phenotype will be compared between preoperative and postoperative tumor tissue and peripheral blood. Appendix C details the complete CyTOF panel that will be used for each individual specimen. Substudies will include:

a. Changes in T-cell subset (CD4, CD8, FoxP3) frequency and memory and activation phenotype (CD25, CD127, CD45RA, CD62L, CCR4, CCR6, Tim1)

b. Changes in T-cell polarization state (intracellular interferon-gamma, TNF-alpha, IL-17, IL-2)

c. Changes in myeloid cell composition: dendritic cells, macrophage, MDSC, neutrophil (HLA-DR, CD11c, BDCA-1, BDCA-2, BDCA-3, BDCA-4, CD68, CD163, CD206, CD66b, CD15)

d. Changes in NK cell and NK T-cell composition (CD56, CD3, V224, Vbeta11)

9) Bone marrow biomarker immune response to MEDI4736 or MEDI4736 + tremelimumab. CyTOF will be used to compare immune cell composition and phenotype, as outlined above in number 8, in the bone marrow (from a routinely resected sixth rib) from patients treated with MEDI4736 or MEDI4736 + tremelimumab, and untreated controls.

3) Tumor and peripheral blood immune cell expression of PD-1 and CTLA-4

a. CyTOF will be used to compare PD-1 and CTLA-4 expression on specific immune cell and non-immune cell populations.

4) Tissue immune gene expression in response to MEDI4736 or MEDI4736 + tremelimumab

a. NanoString gene expression arrays will be used to compare gene expression of 300 immune-related genes in tumor tissue obtained preoperatively and postoperatively

9. 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.

9.1.1 Safety Parameters

9.1.1.1 Definition of adverse events

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

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

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

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical

event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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

9.1.2 Definition of serious adverse events

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

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

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

9.1.3 Definition of adverse events of special interest (AESI)

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 and tremelimumab safety profile and require close monitoring and rapid communication by the investigator to the sponsor. MEDI4736 and

tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

MEDI4736, an anti-PD-L1 antibody, and tremelimumab, an anti-CTLA-4 antibody both belongs to a new class of anticancer therapies, called "checkpoint-inhibitors" that amplify antitumor immune responses by blocking inhibitory signaling pathway modulated by the co-inhibitory or co-stimulatory receptors, PD-1 and CTLA-4 and, expressed on T cells (Callahan and Wolchok, 2013). This class of drugs can have a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organs of the body. Based on this mechanism of action of MEDI4736 and related molecules Adverse events of special interest include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neuropathy and pneumonitis as well as infusion related reactions, serious allergic reactions and anaphylaxis.

9.1.3.1 Pneumonitis

Immune-mediated pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma that may be result of off-target effects of checkpoint inhibitors against the normal lung parenchyma. (Chow, 2013) Presentations of pneumonitis range from asymptomatic lung infiltrates to a mimic of severe bacterial pneumonia. For symptomatic patients, complaints and findings may include dyspnea, cough, tachypnea, pleuritic chest pain, and hypoxia.

Because pneumonitis can quickly escalate and become fatal, early recognition is essential. Initial workup includes chest imaging; however, pneumonitis can have highly variable appearances on chest CT scans. In patients with pulmonary metastases or cardiopulmonary comorbidities, evaluation can be particularly challenging as it can be difficult to differentiate between infection, early pulmonary edema, alveolar hemorrhage, immune-mediated pneumonitis, immune-related tumor inflammation, and tumor progression (Topalian et al, 2012). Pneumonitis has also been reported as a complication of cancer treatment associated with lung and breast cancer.

As of the DCO dates for the IB, pneumonitis including ILD was reported at a frequency rate of Common (44/1645; 2.7%). Most were non-serious and Grade 1 or 2 in severity. CTC Grade 3 pneumonitis was reported in 7 patients (0.4%); CTC Grade 4 in 2 patients (0.1%) and CTC Grade 5 pneumonitis in 2 patients (0.1%). CTC Grade 3 ILD was reported in 3 patients (0.2%). There were no CTC Grade 4 or 5 events of ILD.

In the durvalumab + tremelimumab combination in patients receiving 20 mg/kg durvalumab iv Q4W and 1 mg/kg tremelimumab, pneumonitis including ILD was reported at a frequency of Common (14/560; 2.5%). Most events were CTC Grade 1 or 2. CTC Grade 3 pneumonitis was reported in 3 patients (0.5%). There were no reports of CTC Grade 4 or 5 pneumonitis reported and no Grade 3 or higher ILD events in the combination patients.

Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia (Teply and Lipson 2014). Early consideration of pneumonitis should be realized when patients present with new onset or worsening of respiratory symptoms such as dyspnoea or cough. Prompt treatment with steroids is important as per current established toxicity management guidelines.

9.1.3.2 Infusion-Related Reactions, Anaphylaxis and Allergic Reactions

Adverse reactions that occur during or shortly after infusion may include fever, chills, hypotension, dyspnoea, tachycardia, cyanosis, respiratory failure, urticarial and pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension rash, headache, flushing, sweating, myalgia, nausea, vomiting, unresponsiveness, and haemodynamic instability. The typical onset can be within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10% and 30% occur during subsequent treatments (Lenz 2007).

Anaphylaxis is a systemic, immediate hypersensitivity reaction that is mediated by interactions between factors released from IgE and mast cells; these interactions result in an antigenantibody reaction. Clinical manifestations of acute allergic reactions may range from localised skin reactions at the injection site to AEs, which can include, but are not limited to, those events similar to infusion-related reactions to severe reactions including anaphylaxis, and drug hypersensitivity syndromes, These reactions may be more common with higher rates of infusion, and in patients with a history of allergies.

Across the durvalumab monotherapy and durvalumab + tremelimumab combination therapy programme 37 (2.2%) and 11 (2.0%) patients respectively have experienced either an infusion related reaction or hypersensitivity/anaphylactic reaction. The majority of events were CTC Grade 1 or 2 with 5 patients experiencing a CTC Grade 3 event of infusion related reaction and 1 patient with a CTC Grade 4 event of drug hypersensitivity (all receiving durvalumab monotherapy). There have been no reported CTC Grade 5 events as of the DCO.

Patients participating in durvalumab clinical studies should be closely monitored during and after infusions. Severe hypersensitivity reactions should be managed according to standard clinical practice, and medical equipment and staff trained to treat acute anaphylactic reactions must be immediately available at all sites that perform mAb infusions.

Cytokine release syndrome
Certain mAb therapeutics have been shown to induce a range of acute infusion reactions including cytokine-release syndrome that can lead to AEs in patients. As of the DCO date, there have been no reported events of cytokine release syndrome in the ongoing durvalumab +/- tremelimumab studies.

Immune-complex disease
The potential risk of immune complex disease for durvalumab is theoretical based on the known risk associated with mAbs and other proteins. The incidence of durvalumab ADA-positive patients in clinical studies is low, and hence the risk of immune complex disease is likely to be low.

Specifically, of 1124 patients who were treated with durvalumab 10 mg/kg Q2W and evaluable for the presence of ADAs, 3.3% (37/1124) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 0.3% (3/1124) patients. The presence of ADAs did not have a clinically relevant effect on PK. In combination with tremelimumab the incidence is 4/60 patients (Study D4190C00006). Studies with tremelimumab also showed a low incidence of ADA. There have been no reported events of immune complex reactions in patients receiving durvalumab monotherapy or in combination with tremelimumab.

Considering the low incidence of immunogenicity of durvalumab and tremelimumab and the lack of clinically apparent immune complex disease to date, samples for ADA monitoring may be collected in studies if clinical AEs consistent with immune complex disease are observed.

For guidance on identifying, evaluating, and treating an imAE please see the toxicity management guidelines included in each of the study protocols.

9.1.3.3 Hepatic function abnormalities (hepatotoxicity)

Immune-mediated hepatitis/hepatic toxicity is the inflammation of the liver. Hepatic AEs induced by PD-1/PD-L1 inhibitors commonly present as asymptomatic increase of AST and ALT, rarely total bilirubin. A proportion of patients may be presenting with fatigue, fever and radiologic appearances including hepatomegaly, periportal lymphadenopathy and periportal oedema (Zhang et al 2016).

As a grouped term, selected hepatic events including laboratory abnormalities were reported at

a frequency of 15.1% (248 patients) across 1645 patients who have received durvalumab monotherapy 10 mg/kg Q2W. Hepatitis events (autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatotoxicity and hepatitis acute) were reported at a frequency rate of Uncommon (14 patients; 0.9%). For 9 of the 14 patients, the events of hepatitis were CTC Grade 3 in severity. There were no Grade 4 events. One patient experienced a CTC Grade 5 event of autoimmune hepatitis. Other AESIs such as hepatic failure (5 patients), jaundice (4 patients) and laboratory abnormality AESIs have been observed, two of which resulted in a fatal outcome (CTC Grade 5 hepatic failure and hyperbilirubinaemia). With the durvalumab + tremelimumab combination patients, there were two reports of hepatitis, 1 CTC Grade 1 hepatitis (1 of 560 patients; 0.2%) and 1 CTC Grade 3 autoimmune hepatitis (0.2%) both of

which were considered treatment-related by the reporting investigator. Additionally, there was 1 report of non treatment-related Grade 2 hepatic failure.
Monitoring liver function tests while receiving study medication is important as hepatitis often manifests as asymptomatic elevated levels of hepatic transaminases (ALT, AST, bilirubin; Kim et al 2013). Prompt treatment with steroids is important as per current established toxicity management guidelines.

In Ipilimumab-treated patients, clinical manifestations of hepatitis included nonspecific symptoms of mild fever, general weakness, fatigue, nausea and/or abdominal pain. In the absence of clinical symptoms, treatment-emergent hepatitis presented asymptomatically as elevated hepatic transaminases. Ultrasonograms of the liver can appear normal or may demonstrate homogenous hepatomegaly, edema, or enlarged perihepatic lymph nodes. Biopsy of the liver most commonly shows a diffuse T-cell infiltrate. Other reported pathology patterns include inflammation focused around either hepatocytes or bile ducts.

If subject presents with liver dysfunction, a high suspicion for irAE hepatitis is warranted, however, it is important to distinguish treatment-related toxicity and rule out other causes of hepatic injury, such as infection, preexisting medical conditions, immunosuppression, metabolic or cardiovascular derangements, other medications, or tumor progression.

9.1.3.4 Rash/Dermatitis

Immune-mediated dermatitis is generally mild and presents as mild local or diffuse maculopapular, erythematous rash on the trunk or extremities, which may be accompanied by pruritus, alopecia, and vitiligo, suggestive of inflammatory response to melanocytes

(Lacouture et al 2014). In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or haemorrhagic manifestations (Tarhini 2013, Kaehler et al 2010).

AESIs of rash (as a composite term) were reported as Very common in 199 (12.1%) patients receiving durvalumab monotherapy and Very common in 124 (22.1%) patients receiving the combination. The majority of events were CTC Grade 1 or 2, with 7 and 4 patients, respectively, experiencing CTC Grade 3 events.

AESIs falling under the grouped term of dermatitis that include milder events such as pruritus, eczema and erythema to more specific or severe skin toxicities such as events of dermatitis bullous, dermatitis exfoliative or dermatitis psoriasiform, have been observed with durvalumab monotherapy. Overall, the range of these events have been reported at a frequency of Very common (n=237; 14.4%) in monotherapy treated patients and patients receiving durvalumab + tremelimumab combination (n=114; 20.4%). However, most events were CTC Grade 1 in severity with 3 patients and 4 patients experiencing CTC Grade 3 events in the monotherapy and combination treated groups respectively.

Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.

Pathologic evaluations of biopsy specimens of affected skin often demonstrate eosinophilic infiltration or leukocytoclastic vasculitis; or, they may reveal a lymphocytic predominance characterized by CD8+ T cells, sometimes with tropism for melanin-containing cells. Specifically, in metastatic melanoma patients, the rash associated with immune-checkpoint inhibitors may be indicative of immune response to melanocytes and may progress to vitiligo in some cases. Biopsies showed severe dermatitis with papillary dermal edema, sometimes accompanied by perivascular lymphocytic infiltrate.

Guidelines for the management of subjects with immune-mediated events including dermatitis are outlined in Section 6.6.1.

9.1.3.5 Colitis

Diarrhoea is the most frequent AESI reported across the Phase I to Phase III clinical studies with durvalumab monotherapy, as of the DCO dates for this IB with a frequency of Very common (263/1645; 16.0%) in patients receiving 10 mg/kg durvalumab iv Q2W. Most of thesewere CTC Grade 1 in severity. Treatment-emergent colitis-type AESIs were reported at a

frequency of Common (16 of 1645 patients; 1.0%). Most were CTC Grade 2 or 3. CTC Grade 4 colitis was reported in 1 patient (rare; <0.1%).

In the durvalumab + tremelimumab combination in patients receiving 20 mg/kg durvalumab iv Q4W and 1 mg/kg tremelimumab, diarrhoea was reported at a frequency of Very common (144/560; 25.7%) with most CTC Grades 1 or 2. Colitis was reported at a frequency of Common (26/560; 4.6%). Most colitis events were CTC Grade 3 reported in 17 of the 26 patients on the combination. There were no CTC Grade 4 or 5 cases reported in the combination patients. Patients should be monitored for signs and symptoms of colitis or diarrhoea.

Investigators are instructed to begin diarrhoea management early to minimise the risk of colitis (please refer to the toxicity management guidelines in the study protocols). Early initiation of diarrhea treatment guidelines has been shown to reduce bowel perforation and colectomy rates, drug-related diarrhoea, and serious gastrointestinal imAEs by up to 50% in patients treated with ipilimumab (Tarhini 2013).

9.1.3.6 Endocrinopathy (hypothyroidism, hyperthyroidism, hypopituitarism)

Immune-mediated endocrinopathy is the inflammation of any organ in the hypothalamic pituitary- adrenal axis, but is most typically reported to affect the pituitary, thyroid and/or adrenal glands in patients treated with checkpoint inhibitors, leading to hypophysitis/hypopituitarism, thyroid dysfunction, and/or adrenal insufficiency (Teply and Lipson 2014). The clinical presentation of immune-mediated endocrinopathies most often include hypothyroidism, hyperthyroidism, and nonspecific symptoms of headache and fatigue, but may also include myalgias, visual field defects, behavioural changes, electrolyte disturbances, loss of appetite and hypotension (Tarhini 2013). Patients will generally have abnormal endocrine laboratory test results that include thyroid-stimulating hormone, free T4, total and free T3, cortisol, adrenocorticotrophic hormone, luteinising hormone, folliclestimulating hormone, and testosterone.

Most endocrinopathy events reported were CTC Grade 1 or 2. In the monotherapy pool CTC Grade 3 events consisted of adrenal insufficiency (2 patients), hypophysitis/hypopituitarism (1 patient), hyperthyroidism (1 patient) and hypothyroidism (2 patients). There were no CTC Grade 4 or 5 events. In the combination pool there was a slightly increased incidence of higher-grade events of adrenal insufficiency with 3 patients experiencing CTC Grade 3 and 1 patient with CTC Grade 4 in severiyy. There was 1 patient with CTC Grade 3 hyperthyroidism
and 1 patient with CTC Grade 3 hypophysitis/hypopituitarism.

Prompt initiation of hormone replacement therapy is important for hypothyroidism. Additional guidance for other types of endocrinopathies is provided in the toxicity management guidelines.

Type 1 diabetes mellitus

Type I diabetes mellitus is a heterogeneous disorder characterised by destruction of pancreatic beta cells, culminating in absolute insulin deficiency. The majority of cases are attributable to an autoimmune-mediated destruction of beta cells (type 1a) while a small minority of cases results from an idiopathic destruction or failure of beta cells (type 1b) (Maahs et al 2010). Latent autoimmune diabetes in adults (LADA) is the most common term describing patients with a type 2 diabetic phenotype combined with islet antibodies and slowly progressive betacell failure. Evidence on the occurrence of LADA in relation to adult Type I diabetes mellitus in the general population is usually estimated, due, in part, to limited availability of diagnostic criteria for the LADA (Leslie et al 2006).

Across the monotherapy and combination pool of studies there have been no reported events of type 1 diabetes mellitus. However, 1 patient receiving durvalumab monotherapy in an ongoing phase III randomised clinical study outside of the pooled dataset (<0.1%) experienced Grade 3 type 1 diabetes mellitus. The patient, a 60 year old Caucasian male with NSCLC without a history of diabetes mellitus or hyperglycemia, developed severe autoimmune-mediated hyperglycemia (blood glucose 458 mg/dL) 43 days after starting durvalumab, was tested positive for anti-GAD antibody 322 U/mL (reference range 0 to 5 U/mL) and was negative for B-islet antibody. He was diagnosed with type 1 diabetes mellitus by an endocrinologist. The type 1 diabetes mellitus was treated with insulin and resolved with sequelae (insulin dependency).

For patients with suspected diabetes mellitus investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin. Also please refer to the endocrinology section of the toxicity management guidelines in the study protocols.

Nephritis

The major clinical syndromes produced by immune-mediated renal injury include nephrotic syndrome, rapidly progressive glomerulonephritis, and acute renal failure (Cunard and Kelly 2003). In association to immune-checkpoint inhibitors, two different forms of ipilimumabinduced renal damage are reported, acute kidney injury due to predominant acute granulomatous tubulointerstitial nephritis and nephrotic syndrome in lupus nephritis (Izzedine et al 2014). Signs and symptoms include increase in serum creatinine, decrease in urine output, peripheral oedema, haematuria, loss of appetite.

As a grouped term, selected renal events including laboratory abnormalities were reported at a

frequency of 5.3% (87 patients) across the 1645 patients included in the durvalumab monotherapy pool. Nephritis events were reported at a frequency rate of Uncommon (5 patients; 0.3%) with 1 CTC Grade 2 autoimmune nephritis, 1 CTC Grade 2 glomerulonephritis, 2 CTC Grade 2 nephritis and 1 CTC Grade 3 tubulointerstitial nephritis. There was 1 CTC Grade 3 nephritis reported in the 560 (0.2%; Uncommon) patients in the durvalumab + tremelimumab combination pool. An additional AESI of acute kidney injury was reported in 26 patients (1.6%) receiving durvalumab monotherapy and 7 patients (1.3%) in the combination pool, 1 of which was CTC Grade 5 in severity; the event was considered not treatment-related by the reporting investigator.

Patients should be monitored for changes in renal function (eg, that manifest as elevated serum blood urea nitrogen and creatinine, decreased creatinine CL, electrolyte imbalance, decrease in urine output, or proteinuria and any other findings that may be indicative of nephritis) prior to and periodically during treatment. Prompt treatment with steroids is important as per current established toxicity management guidelines in the study protocols.

9.1.3.7 Neuropathy/Neuromuscular Events (to include MG and GB)

Neuromuscular toxicity is relatively uncommon but may manifest as a mild peripheral sensory neuropathy or muscle weakness. Although they are rare, severe neuropathies and myopathies have been observed. Emergent cases of neuropathy can present with Guillain-Barré syndrome, transverse myelitis, or myasthenia gravis, among other diagnoses. Depending on presentation, patients may require neuroimaging, nerve conduction studies, and, potentially, nerve or muscle biopsy to arrive at the diagnosis (Teply and Lipson 2014). Isolated cases of myasthenia gravis have been reported in studies combining anti-PD-1/PD-L1 mAb with anti-CTLA-4 mAb (Naidoo et al 2015).

As of the DCO for this IB there have been no reports of Guillain-Barre syndrome or Myasthenia Gravis in patients receiving durvalumab monotherapy. Two patients receiving the durvalumab + tremelimumab combination have reported a case of Myasthenia Gravis but none at the recommended dose of 20 mg/kg durvalumab iv Q4W and 1 mg/kg tremelimumab.

Prompt treatment of these conditions as per current toxicity management guidelines is important. Patients should be monitored for signs and symptoms that may include peripheral sensory neuropathy, muscle weakness, peripheral neuropathy including numbness, tingling, and
sensitivity to touch.

Neuropathies associated with ipilimumab have been difficult to assess because these irAEs are transient and present with vague symptoms. Presentations of neurotoxicity may include a mild peripheral sensory neuropathy or muscle weakness. Symptoms of peripheral neuropathy

include numbness, tingling, paresthesia (pins and needles sensations), sensitivity to touch, or muscle weakness. In patients with extreme symptoms, they may present with burning pain, muscle wasting, paralysis, or organ dysfunction. Symptoms are typically detected with physical examination findings ranging from sensory changes to loss of deep-tendon reflexes.

Depending on presentation, patients may require neuroimaging, nerve conduction studies, and, potentially, nerve or muscle biopsy to arrive at the diagnosis.

Pancreatitis

Pancreatitis is an inflammatory condition of the pancreas that typically manifests initially as asymptomatic elevations of amylase and lipase in patients treated with immune checkpoint inhibitors. Clinical presentation frequently includes low-grade abdominal pain with accompanying fever and malaise (Weber et al 2012, Di Giacomo et al 2010). Biopsies showed diffuse T-cell infiltrate consistent with immune-mediated pancreatitis (Weber et al 2012).

Across the 1645 patients in the monotherapy program, events of pancreatitis were Uncommon to rare. Two patients (0.1%) experienced pancreatitis (CTC Grade 3 and Grade 4 in severity) and 1 patient (<0.1%) with CTC Grade 3 acute pancreatitis. Elevations in amylase and lipase were reported at a frequency rate of Common (0.4% and 0.4%, respectively). In ongoing sponsored studies with durvalumab + tremelimumab therapy in 560 patients, events of pancreatitis were Uncommon; pancreatitis was reported in 4 patients (0.7%) with 3 of these CTC Grade 3 in severity and acute pancreatitis in 1 patient (0.2%). Elevations in amylase and lipase were reported at a frequency of Common (6.1% and 7.0%, respectively). Patients should be monitored for signs and symptoms of pancreatitis including Grade 3 or 4 elevations in lipase and/or amylase.

Prompt treatment of this condition as per current established toxicity management guidelines is important.

Other Potential Risks
Serious Infections
Serious and/or ≥ Grade 3 infections requiring hospitalisation including, but not limited to, sepsis, pneumonia, lung infections, have been reported in clinical studies with durvalumab, but are often confounded by underlying disease and use of concomitant medications (ie, steroids and other immunosuppressives) that may cause opportunistic infections. As of the DCO, events from the MedDRA Infections and Infestations SOC, events with a severity ≥Grade 3 and frequency of ≥1% included lung infection (n=16; 1%), pneumonia (n=39; 2.4%), sepsis (n=26; 1.6%) and urinary tract infection (n=20; 1.2%). CTC Grade 3 events were reported in 98 patients (6.0%), CTC Grade 4 events were reported in 25 patients (1.5%) and CTC Grade 5 infection events in 15 patients (0.9%). Across the durvalumab + tremelimumab combination program, patients experiencing ≥Grade 3 infections at a frequency

of ≥1% included lung infection (n=9; 1.6%), pneumonia (n=14; 2.5%), sepsis (n=6; 1.1%) and urinary tract infection (n=9; 1.6%). CTC Grade 3 events were reported in 50 patients (8.9%), CTC Grade 4 events were reported in 2 patients (0.4%) and CTC Grade 5 infection events in 4 patients (0.7%). Patients should be monitored for serious infections while receiving durvalumab.

9.2 Assessment of safety parameters

9.2.1 Assessment of severity

Severity will be graded according to the NCI CTCAE v4.03.The determination of severity for all other events not listed in the CTCAE will 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 the severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

9.2.2 Assessment of relationship

In this study, patients will receive one infusion of MEDI4736 either alone or in combination with tremelimumab. The remaining procedures to be conducted in this study will follow standard of care for the treatment of patients with surgically resectable MPM. The study investigators will carefully monitor subjects to determine whether adverse events are related to the infusion of study drug or are expected complications of standard clinical procedures.

9.3 Recording of adverse events and serious adverse events

Adverse events associated with the investigational product will be recorded in an adverse event log maintained by the principal investigator using a recognized medical term or diagnosis that accurately reflects the event. Adverse events associated with the investigational product 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 associated with the investigational product:

- 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 MEDI4736 (yes or no), tremelimumab (yes/no)
- Action taken with regard to MEDI4736/tremelimumab
- Outcome

In addition, the following variables will be collected for SAEs associated with the investigational product as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

Causality assessment in relation to tremelimumab
Events that are unequivocally due to disease progression will not be reported as an AE during the study.

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

Adverse events and serious adverse events associated with the investigational product will be recorded from the time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of MEDI4736).

During the course of the study all AEs and SAEs associated with the investigational product will be proactively followed up for each subject. Every effort will 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-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 associated with the investigational product 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 associated with the investigational product 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 adverse event log. 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) associated with the investigational product 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 associated with the investigational product occurring in former study subjects after the 90-day safety follow-up period for patients treated with MEDI4736 or MEDI4736 + tremelimumab. However, if the investigator learns of any SAEs associated with the investigational product, 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 will notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

9.3.2 Reporting of adverse events

Any adverse events or toxicities that are determined to be related to surgery should NOT be reported unless they are unusual.

Such AEs common following surgical resection by EPP or PD can occur within the hospital stay immediately following surgery, or can persist once the patient is discharged and seen in the outpatient clinic postoperatively. Such AEs may include:

1) Chest pain or incisional pain
2) Hypotension (including orthostatic hypotension)
3) Tachycardia
4) Atrial fibrillation (or other atrial arrhythmia)
5) Dsypnea
6) Anorexia, or loss of appetite
7) Anemia
8) Hyponatremia
9) Hypernatremia
10) Hypokalemia

11) Hyperkalemia

12) Hypomagnesemia

13) Increased creatinine

14) Leukocytosis

15) Acidosis

9.3.3 Reporting of serious adverse events

All SAEs associated with the investigational product will be reported, whether or not considered causally related to the investigational product.The reporting period for SAEs associated with the investigational product is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of MEDI4736 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 associated with the investigational product as per local requirements.

The investigator and/or sponsor must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events associated with the investigational product 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-##-#####)

***** 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 associated with the investigational product becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events associated with the investigational product 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.

9.3.3.1 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of MEDI4736 or 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 MEDI4736 safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

9.3.4 Other events requiring reporting

9.3.4.1 Overdose

An overdose is defined as a subject receiving a dose of MEDI4736 or tremelimumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with MEDI4736 or 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 10.1.2 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of MEDI4736 or tremelimumab.

The investigator will use clinical judgment to treat any overdose of MEDI4736 or MEDI4736 + tremelimumab.

9.3.4.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.3) 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.

9.3.4.3 Pregnancy

Pregnancy itself, or pregnancy of a subject's partner, is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 any conception occurring from the date of the first dose until 90 days after the last dose (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study.

Pregnancy in a female subject who has received investigational product 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).

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to AstraZeneca/MedImmune Patient Safety or designee after outcome.

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days following the last dose of monotherapy MEDI4736 or for 180 days following the last dose of combination therapy with MEDI4736 and tremelimumab.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to AstraZeneca/MedImmune Patient Safety or designee using the Safety Fax Notification Form for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

This is a pilot study designed to show that combination therapy with MEDI4736 and tremelimumab can have a substantial impact on surgically resectable MPM patients. All subjects will be randomized after the mediastinoscopy + thoracoscopy to one of the three arms to receive MEDI4736+tremelimumab, MEDI4736 only, or untreated control. The primary endpoint will be the ratio of intratumoral cytotoxic T cells to regulatory T cells (CD8/Treg) before and after treatment. The secondary endpoints are the percentage of inducible T-cell co-stimulator (ICOS) positive intratumoral CD4 T cells and tumor tissue expression (Ventana assay) of programmed death-ligand 1 (PD-L1) before and after each treatment. Overall and recurrence-free survival will be also measured as the secondary endpoint. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients. All subjects will undergo surgical resection One to six weeks after the infusion.

10.1 Sample size

10.2 The primary objective is comparison of the ratio of CD8/Treg before and after treatment with combination MEDI4736+Tremelimumab. A total of 20 evaluable subjects (if tissue obtained) will be enrolled in this study for 24 months and 8 subjects will be assigned to combination MEDI4736+Tremelimumab (8 subjects to MEDI4736 only and 4 subjects to control). The outcome of interest in this study is a change in ratio of CD8/Treg before and after treatment with combination MEDI4736+Tremelimumab within subjects. There are no data available to estimate a change of ratio of CD8/Treg before and after the treatment but in our pilot data from 6 subjects with MPM the log transformed ratio of CD8/Treg was approximately normally distributed with a mean of 1.94(6.96 in raw scale) and standard deviation of 0.808(2.24 in raw scale). Assuming that repeat values are moderately correlated(r=0.5), then the difference between before and after the combination treatment will also have a standard deviation of 0.808(2.24 in raw scale). We estimate that we will have 80% power (alpha=5%, a paired t-test) to detect an increased log ratio CD8/Treg of 2.87(17.71 in raw scale) after the combination treatment with 8 subjects.

10.3 Analysis plan

There will be two treatment arms (MEDI4736 only and combination MEDI4736+tremelimumab) and one untreated arm (control). Randomization, stratified by receiving previous chemotherapy or not, will help to minimize patient selection biases between three arms. Preliminary tests will be performed to assess whether our data is normally or non-normally distributed. Patient characteristics will be summarized descriptively. Baseline characteristics will be compared by treatment assignment. For our primary objective that compares outcome variable in tissues before and after treatment with combination MEDI4736

and tremelimumab, we will use a paired t-test in log-transformed ratio of intratumoral cytotoxic T cells to regulatory T cells (CD8/Treg) before and after the treatment. In our secondary objective numerous variable comparisons are made between tumor tissues from untreated patients with from patients undergoing treatment with either MEDI4736 or MEDI4736 + tremelimumab, and between tumor tissues from patients undergoing treatment with MEDI4736 and tumor tissues from patients undergoing treatment with MEDI4736+tremelimumab. In these comparisons, a paired t-test or Student t-tests will be performed. Because approximately 20 comparisons of immune cell populations will be performed, a Bonferroni correction will be applied to correct for multiple comparisons. For the comparison of overall survival and recurrence-free survival between treatment groups, log-rank test will be used. These analysis will be post-protocol analysis based upon data obtained from the standard of care follow up in our post-surgical patients. SAS software will be used for all other statistical analyses.

11. ETHICAL AND REGULATORY REQUIREMENTS

11.1 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.

11.2 Ethics and regulatory review

MEDI4736 and tremelimumab are both investigational drugs not approved for clinical use in patients with surgically resectable MPM. Our study will undergo review by the Baylor College of Medicine Institutional Review Board. Investigational New Drug applications will also be filed with the FDA.

11.3 Informed consent

Informed consent shall be documented by the use of a written consent form approved by the IRB and the sponsor and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

11.4 Changes to the protocol and informed consent form

Any changes to the protocol or informed consent form will be reviewed by the sponsor and the local IRB prior to implementation. Any changes to the informed consent form that impact currently enrolled subjects (e.g., changes in procedures, changes in the benefit/risk profile) will require that subjects are re-consented with the new consent form.

11.5 Audits and inspections

All records and documents pertaining to the study will be maintained in appropriate permanent files as per the ICH guidelines for Essential Documents for the Conduct of a Clinical Trial and 21 CFR 11, and will be available for inspection by the Sponsor, Sponsor designee, the FDA, or any other designated review body at any time.

12. STUDY MANAGEMENT

The principal investigator assumes all oversight and reporting of the study, including the training of study site personnel and monitoring of the study.

12.1 Training of study site personnel

The PI of this study will train the study coordinator in the procedures necessary to identify and accrue appropriate individuals to the study. The PI of the study will also train the staff scientist in the lab appropriate tissue collection and storage procedures. The co-investigator of this study, Dr. Jun Zhang, will train infusion center staff on appropriate administration of study drugs.

12.2 Monitoring of the study

12.2.1 Source data

Subjects will be monitored closely throughout the course of the study with regular visits with the Study PI and direct access to the PI throughout the duration of the study. The PI is directly responsible for the study subjects, and the study staff will be instructed to contact the PI immediately with any concerns regarding patient safety or other matters.

12.3 Study timetable and end of study

The end of the study will be defined as the time point 90 days after the final subject receives the infusion of study drug. The recruitment period will take place over a period of 24 months.

13. DATA MANAGEMENT

The database that will be utilized for data collection and storage will be OnCORE. The PI and study staff will adhere to the reporting requirements of the data to the institutional IRB.

To ensure the privacy and confidentiality of data for this protocol, the data will be stored on a restricted access location on our institution's server. Access to the project directory containing the data will be limited to the investigators and research staff. Information about data security awareness is promoted through user training and education and supplemented by policies and procedures. Password protection will be used for all transactions that involve viewing, editing, and analyzing the data or that provide access to data fields derived from the original source documents.

The investigator maintains the confidentiality standards of each patient enrolled in the study through the assignment of a unique subject identification number that de-identifies the study information from the patient's health information. The key linking subject code to the patient is kept in an additional secure restricted access location on our institution's server that is only accessible to the study staff. No identifying information, such as the patient's name, will be included in the data sets used for reporting the data. The data released to Astrazenica will be patient age, histology, and chemotherapy status, as well as CyTOF data, PD-L1 immunohistochemistry data, and nanostring mRNA data. Patient medical information obtained for the study is confidential, and may only be disclosed to third parties as permitted in the Informed Consent Form signed by the subject unless permitted or required by law.

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APPENDIX A: MEDI4736 DOSE CALCULATIONS

MEDI4736 Dosing

The MEDI4736 dosing should be done depending on subject weight:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

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

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL) where 50 mg/mL is MEDI4736 nominal concentration

The corresponding volume of MEDI4736 should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle only needed for greater than 10% change in weight.

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

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

Example:

1. Cohort dose: 10 mg/kg

2. Subject weight: 80 kg

3. Dose for subject: 800 mg = 10 (mg/kg) × 80 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 800 mg / 50 (mg/mL) = 16.0 mL

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

Number of vials = 16.0 (mL) / 10 (mL/vial) = 2 vials

APPENDIX B

Schedule of study procedures: follow-up for subjects who have completed MEDI4736 or MEDI4736 plus Tremelimumab but did not have resection.

Evaluation	Time Since Last Dose of MEDI4736							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
Urine hCG or serum βhCG	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
<<World Health Organization>> <<ECOG>> performance status	X	X	X		X (and month 9)			X
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					X
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[b]	X							

[a] Full physical exam

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

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

APPENDIX C: CyTOF Antibody Panel including cell definitions

Cell Type	**Definition**	**Subset or Activation Markers**
Viability	Cisplatin-	
Immune cell	CD45+	
T cell	CD3+	CD4, CD8, FoxP3, CD25, CD127, CD45RA, CD62L, ICOS, CCR4, CCR6, Tim1
Dendritic cells	HLA-DR+, CD3-, CD14-, CD19-, CD56-	BDCA-1, BDCA-2, BDCA-3, BDCA-4, CD16
MDSC	CD11b+, CD15+	
Macrophage	CD68+	CD163, CD206
Monocyte	CD14+	CD16
B	CD19+	HLA-DR, CD27, CD38
NK	CD56+, CD3-	CD314, CD69
NKT	V224+, Vbeta11+	
PMN	SSC hi, CD15+	CD66b
RBC	CD235a/b	
Platelet	CD61+	
Tumor cell	CD45-	
All cells		PD-1, PD-L1, CTLA-4
All myeloid cells		HLA-DR, CD40, CD80, CD86, ICOSL
T cell polarization		interferon-gamma, TNF-alpha, IL-17, IL-2
Other		Ki-67