AstraZeneca

Clinical Study Protocol

Drug Substance	Tremelimumab and MEDI4736 (Durvalumab)
Study Code	D4884C00001
Version	4.0
Date	13 Sep 2018

A Phase II, Multi-Center, Open-Label Study of Tremelimumab Monotherapy in Patients with Advanced Solid Tumors

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT Number: 2015-002934-32

VERSION HISTORY

Version 4.0, 13 Sep 2018 Changes to the protocol are summarised below,
Key Procedure and Major changes: **1.** Protocol Synopsis and Section 8.5: Add final data cut-off (DCO) of OS and safety approximately 6 months after the primary analysis data cut-off. **2.** Section 6.3.12: Update to safety data collection following the final DCO of the study. **3.** Section 7.2.3: Provide clarification on patient management post final DCO for those patients still in treatment of investigational product. **4.** Section 7.8: Update as some wording moved to/reflected in the section 7.2.3.

Version 3.0, 25 Jan 2018 Changes to the protocol are summarised below,

Key Procedure and Major changes:

1. Protocol Synopsis and Section 8.5: Update to data cut-off (DCO) for the primary analysis.
2. Section 1.2.2: Update to patient number exposed to the entire clinical development program as of DCO date 12 July 2017.
3. Section 1.3.2, 1.3.2.1, 1.3.2.2 and 1.3.2.3: Update to overall potential risks and risks in dfferent regimens for Tremelimumab, MEDI4736 and MEDI4736 + tremelimumab.
4. Section 6.3.12: Update to safety data collection following the final DCO of the study.
5. Section 6.5: Changed from Overdose to Adverse Events of Special Interest. All subsequent sections were renumber accordingly.
6. Section 6.8, 6.8.1: Update to management of investigational product-related toxicities.
7. Section 7.2.3: Provide clarification on patient management post final DCO for those patients still in treatment of investigational product.
8. Section 7.8: Delete “either on the current study or an alternate roll-over study” from the parapraph as the description is not applicable per current status.
9. Section 8.5.6: Delete “Details regarding biomarker-defined subgroups and associated analyses will be provided in the SAP”.
10. Appendix E: Updates to Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion related, and Non Immune-mediated Reactions.

Version 2, 09 May 2016
Changes to the protocol are summarised below,

1. **Key Procedure and Major changes:**

   1) The sPD-L1 sample collection is removed from the protocol as the sample will not be tested from scientific need. The following sections of the protocol have been amended to reflect this change: Section 2.4; Section 5.5, Section 7.2.2, Table 2, and Table 3.

   2) Section 3.1 Inclusion Criteria 8: Revise Calculated Creatinine Clearance to ≥30 mL/min and add measured 24-hour urine collection for determination of creatinine clearance, which will allow for evaluation of MEDI4736 in a broader UBC patient population that may be more representative of a real world population.

   3) Section 3.2 Add exclusion criteria 3: Prior randomisation or treatment in a previous MEDI4736 and/or tremelimumab clinical study regardless of treatment arm assignment to exclude patients who have participated in prior MEDI4736/Treme studies (eg. Danube).

   4) Section 3.2: Exclusion criteria 7, the timeline of major surgical procedure (as defined by the Investigator) prior to the first dose of IP is extended from 21 days to 28 days.

   5) Section 3.2: Exclusion criteria 15, for brain metastases or spinal cord compression, allow patients to be enrolled unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 14 days prior to study treatment.

   6) Section 3.2 Exclusion criteria 18, give clarification on active infection.

   7) Triplicate ECGs is deemed unnecessary during the screening. This change will simplify the screening procedure and benefit the patients whose results are normal in the first single ECG. The following sections of the protocol have been amended to reflect this change: Section 3.2 exclusion criteria 16, Table 2, footnote d, Section 5.2.3.

   8) Section 3.9.1, (Procedures for discontinuation of a patient from investigational product) was revised to recommend the investigator discuss a patient's case with AstraZeneca prior to discontinuing the patient from study therapy. This change was made to ensure appropriate action will be taken regarding the patient's care and treatment.

Version 2, 09 May 2016
Changes to the protocol are summarised below,

9) Section 4, Table 2, footnote i, give explanation to "prior to treatment with any IP" and the pre-dose PK may not exceed 6 hours prior to start of infusion, clarify a follow up PK sample collection for tremelimumab is required for MEDI4736+tremelimumab combination therapy at week 24.

10) Give the timeline that study treatment should begin within 3 days of registration which reflects the actual status in clinical sites. The following sections of the protocol have been amended to reflect this change: Section 4, Table 2, footnote k and section 3.3.

11) Reflect the move of Biobank in the UK to Fisher. The following sections of the protocol have been amended to reflect this change: Section 5.4.3, Section 5.5 and Section 5.5.

12) Remove the toxicity management guideline from section to CSP appendix. The following sections of the protocol have been amended to reflect this change: Section 6.7 and Appendix.

13) Modified the relevant languages for patients' access to study treatments post Study in section 7.8

14) Section 8.3 give clarification on the evaluable analysis set and the FAS.

15) Section 8.5 add evaluable analysis set as an analysed method for efficacy data.

2. Minor changes for clarifying and correction of previous version:

1) Add word "approximately" before 32 evaluable patients. The following sections of the protocol have been amended to reflect this change: Protocol synopsis, Section 1.4 and Section 8.2.

2) Give clarification if the PD is unequivocal/symptomatic, the investigator may elect not to confirm PD depending on the status of the patient before sequencing. The following sections of the protocol have been amended to reflect this change: Section 1.4, Section 4, Section 5.1, Section 7.2.2 and Section 7.2.3.

Version 2, 09 May 2016
Changes to the protocol are summarised below,

3) Give clarification on the timeline of data cut-off for the primary analysis and final data cut-off. The following sections of the protocol have been amended to reflect the clarification: Protocol synopsis and Section 8.5.

4) Section 3.1 Combine inclusion criteria 3 and 4 as one point under inclusion criteria 3.

5) Section 3.1 Inclusion criteria 5: Include the reference section for ECOG performance status.

6) Section 3.1: Inclusion criteria 9
Add "underwent surgical sterilization (bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy)" under the inclusion criteria.

7) Section 3.2: Exclusion criteria 11 for active or prior documented autoimmune or inflammatory disorders, add 2 more exceptions to this criterion.

8) Section 3.2 Exclusion criteria 12, add one more condition "serious chronic GI conditions assocated with diarrhea" in the criteria that would interfere with evaluation of IP or interpretation of patient safety or study results.

9) Section 3.2 Exclusion criteria 22, the patient will be excluded if has known allergy or hypersensitivity to IP or any IP excipient.

10) Section 3.3 add the requirement for tumor biopsy collection timeline, location and also the quantity should be taken care during collection.

11) Section 3.8 add the title "Female patient of child bearing potential" and "Male patient with a female partner of child bearing potential".

12) Section 4, Table 3, footnote a&b, give clarification on the schedule time of follow up period. Footnote i &j, clarify that the PK, ADA, circulating soluble factors, gene expression & PBMC assessments, do not need to be collected during retreatment follow-up period.

Version 2, 09 May 2016 Changes to the protocol are summarised below,
13) Section 5.1, add "All on-study assessments should utilize the same mode of scanning (CT or MRI) as baseline scans for accurate comparisons" to emphasize the sam mode's importance. 14) Section 5.1, clarify that in addition to the required confirmatory scan for PR and CR, it is also required following the initial demonstration of PD. 15) Section 5.1, clarify the time for 2 months is 8 weeks and update "AstraZeneca" instead of "the Sponsor". 16) Section 5.2.4, clarify the BP can be measured in supine or semi-supine position. 17) Section 5.5.1 clarify for the collection of tumor biopsies at study treatment discontinuation is optional, including the disease progresses on MEDI4736-based regimens. 18) Section 5.5.3 clarify the storage period of samples to be in line with section 5.4.3. 19) Section 6.1 calrify the definition for AE. 20) Section 7.2.1 clarify for MEDI4736 monotherapy, see figure 6. 21) Section 7.2.2 language is being clarified to state that written informed consent to retreatment will be obtained in the setting of PD. 22) Section 7.2.2 update the singular target lesion to plural target lesions and also clarify the confirmed response that is CR or PR. 23) Section 7.2.3 delete the sentence "prior to designation as a DLT".

Version 1, 06 July 2015
Initial creation

This Durvalumab Protocol template has been to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Phase II, Multi-Center, Open-Label Study of Tremelimumab Monotherapy in Patients with Advanced Solid Tumors

International Co-ordinating Investigator

PPD

Study site(s) and number of subjects planned

The study will screen up to approximately 38 patients with each selected advanced solid tumor type in order to enroll approximately 32 evaluable patients with each tumor type who will receive tremelimumab monotherapy, with the option for eligible patients to be sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after progressive disease (PD).

Study period		Phase of development
Estimated date of first subject enrolled	Q4 2015	II
Estimated date of last subject completed	Q2 2018	II

Study design

This is an open-label, multi-center study to determine the efficacy and safety of tremelimumab monotherapy in the treatment of different cohorts of patients with selected advanced solid tumors. If eligible and at the discretion of the Investigator, after confirmed disease progression on tremelimumab monotherapy or during follow-up, patients will have the option of being sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, for up to 12 months or until disease progression, whichever comes sooner. For each tumor cohort, a minimax Simon 2-Stage design will be used to stop recruitment early if no response is observed in the first stage and thus reduce patient exposure to non-active treatment. If 1 or more responses are observed in the first 20 treated patients with the selected tumor type, an additional 12 patients will be enrolled, for a total of 32 evaluable patients. If no responses are observed, the disease control rate (DCR) data will also be evaluated to make a final decision before discontinuing the tumor cohort. If at least 10 out of the first 20 patients achieve DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients may be enrolled, for a total of 32 evaluable patients. Patients' tumor response and DCR will be monitored on an ongoing basis in order to minimize the time between Stage 1 and Stage 2.

Tumor assessments will be performed as follows for each tumor type (additional tumor types may be added at the discretion of the Sponsor), with categorization of objective tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1):

- Urothelial bladder cancer (UBC) and triple-negative breast cancer (TNBC): Every 8 weeks relative to the date of first infusion of investigational product (IP) until confirmed progression.
- Pancreatic ductal adenocarcinoma (PDAC): Every 6 weeks for the first 48 weeks relative to the date of first infusion of IP and then every 12 weeks (q12w) thereafter until confirmed progression.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the efficacy of tremelimumab monotherapy in terms of ORR	ORR using Investigator assessments according to RECIST 1.1

Secondary Objective:	**Outcome Measure:**
To further assess the efficacy of tremelimumab monotherapy in terms of DoR, DCR, PFS, BoR, and OS	DoR, DCR, PFS, and BoR using Investigator assessments according to RECIST 1.1 OS
To assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow- up in terms of ORR, DoR, DCR, PFS, BoR, and OS	ORR, DoR, DCR, PFS, and BoR using Investigator assessments according to RECIST 1.1 OS

Safety Objective:	Outcome Measure:
To assess the safety and tolerability profile of tremelimumab monotherapy	AEs, physical examinations, laboratory findings, vital signs, and ECGs
To assess the safety and tolerability profile of MEDI4736 monotherapy and of MEDI4736 + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow-up	AEs and laboratory findings

Exploratory Objective:	Outcome Measure:
To assess the PK of tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy	Concentration of tremelimumab and MEDI4736 in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow, sparse sampling)
To investigate the immunogenicity of tremelimumab and MEDI4736	Presence of ADAs for tremelimumab and MEDI4736 (confirmatory results: positive or negative)
To collect blood and tissue samples for defining biological responses to tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy and for identifying candidate markers that may correlate with likelihood of clinical benefit	Protein expression detected by IHC (eg, PD-L1) Circulating soluble factors (eg, cytokines and autoantibodies) miRNA/mRNA T-cell and MDSC phenotyping

Target subject population

Adult patients (age ≥18 years) with advanced and metastatic solid tumors including but not limited to histologically or cytologically documented UBC, PDAC, or TNBC(Additional tumor types may be added at the discretion of the Sponsor.)

Duration of treatment

Treatment with tremelimumab monotherapy will continue for a 12-month period until confirmed PD (unless there is continued clinical benefit per Investigator judgment), unacceptable toxicity, withdrawal of consent, initiation of alternative anticancer therapy, or other reasons to discontinue treatment occur. After confirmed disease progression during treatment with tremelimumab monotherapy or during follow-up, patients who meet the eligibility criteria for sequencing (see Section 7.2.3), at the discretion of the Investigator, may be sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy for up to 12 months or until disease progression, whichever comes sooner. Treatment with sequenced therapy will begin not less than 42 days and not more than 120 days after the last dose of tremelimumab monotherapy. For patients who have confirmed PD during the

tremelimumab monotherapy follow-up period, treatment with sequenced therapy will begin not more than 60 days after confirmed progression. These patients will follow similar assessment schedules to those followed during the initial tremelimumab monotherapy treatment period. Crossover from the MEDI4736 monotherapy group to the MEDI4736 + tremelimumab combination therapy group will not be permitted.

Patients who complete 12 months of tremelimumab monotherapy, or who complete 12 months of MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after sequencing, will enter follow-up. Any of these patients who then develop PD during the follow-up period may restart their treatment for another 12 months with the same treatment guidelines followed previously. In addition, patients receiving combination therapy who complete the 4 dosing cycles with MEDI4736 + tremelimumab (with clinical benefit per Investigator judgment), but subsequently experience progression (according to RECIST 1.1) during treatment with MEDI4736 alone, will be given the option to restart MEDI4736 + tremelimumab combination therapy (see Section 7.2.2). All patients who restart treatment will receive a maximum of 12 months of further treatment. Patients who have discontinued study treatment will enter long-term follow-up.

Investigational product, dosage and mode of administration

Tremelimumab monotherapy:

Tremelimumab 750 mg via intravenous (IV) infusion every 4 weeks (q4w) for 7 doses (cycles), then q12w for 2 additional doses (cycles), for up to a total of 12 months (9 doses [cycles] total)

MEDI4736 monotherapy:

MEDI4736 1.5 g via IV infusion q4w for up to a total of 12 months (13 doses [cycles])

MEDI4736 + tremelimumab combination therapy:

Tremelimumab 75 mg via IV infusion q4w starting on Week 0, for up to 4 cycles

MEDI4736 1.5 g via IV infusion q4w, starting on Week 0, for up to a total of 4 cycles, followed by MEDI4736 1.5 g via IV infusion q4w, starting on Week 16, for up to a total of 8 months (9 additional doses [cycles])

Statistical methods

The primary objective of this study is to assess the efficacy of tremelimumab monotherapy in terms of objective response rate (ORR). ORR (per RECIST 1.1 as assessed by site Investigator) is defined as the number (%) of patients with a confirmed complete response or confirmed partial response and will be based on all treated patients with measurable disease at baseline per site Investigator and will be estimated for each selected solid tumor with corresponding 2- sided 95% exact confidence intervals.

It is estimated that a total of 38 patients in each cohort of selected advanced solid tumor type need to be screened to enroll approximately 32 evaluable patients (ie, evaluable for the primary endpoint).

A minimax Simon 2-Stage design (Simon 1989) will be used according to the following assumptions and algorithms to reduce exposure of a large number of patients to ineffective treatment.

Assumptions:

H0: p0=0.02 (p0: proportion of responders under the null hypothesis)

H1: p1=0.14 (p1: proportion of responders under the alternate hypothesis)

Algorithm:

N=32 evaluable patients, with N_1=20 and N_2=12

If no response is observed out of the first 20 patients, the DCR data will also be evaluated to make a final decision before discontinuing the tumor cohort. (Ongoing patients will still be eligible to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy as previously described.) If ≥10 out of the first 20 patients achieve DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients may be enrolled. A final decision to continue enrollment will be made by the Sponsor after evaluating all of the available clinical data at that time.

If 1 or more responses are observed out of the first 20 patients, enroll 12 additional patients, for a total of 32 evaluable patients in each tumor type.

- If ≤2 responses are observed out of the 32 patients, then no further investigation of that tumor type will be done.
- If >2 responses are observed out of the 32 patients, the null hypothesis will be rejected, and further investigation of that tumor type is warranted.

The assessment of response after the first 20 evaluable patients in the selected tumor types will be based on Investigator/site tumor data RECIST 1.1 assessment. This design will ensure a type I error of no more than 5% (1-sided) and 83% power for each selected tumor type.

Secondary efficacy variables include duration of response (DoR), DCR, progression-free survival (PFS), best objective response (BoR), and overall survival (OS). Efficacy data will be summarized and analyzed based on the Full Analysis Set.

The data cut-off for the primary analysis of all study endpoints including OS, will take place approximately 12 months after the last patient completes 12 months of initial Treme Monotherapy, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor. A final data cut-off of OS and safety will be conducted approximately 6 months after the primary analysis data cut-off.

Kaplan-Meier plots and median DoR, PFS, and OS will be presented. Also, summaries (ie, number of patients [%]) of PFS, death events, and DCR will be provided.

The analysis of ORR, DoR, DCR, BoR, and PFS will be based on site Investigator assessments according to RECIST 1.1 using all scans regardless of whether they were scheduled or not.

In the tremelimumab monotherapy arm only, sensitivity analyses of ORR, DoR, DCR, and BoR may be performed based on site Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

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List of 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
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
$AUC_{(0\text{-}28)day}$	Area under the plasma drug concentration-time curve from time 0 to Day 28 post-dose
β-hCG	Beta-human chorionic gonadotropin
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
C_{trough}	Trough plasma concentration
$C_{trough,ss}$	Trough plasma concentration at steady state
DCR	Disease control rate
DLT	Dose-limiting toxicity

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
fT_3	Free triiodothyronine
fT_4	Free thyroxine
FU	Fluorouracil
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HER-2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
imAE	Immune-Mediated Adverse Event
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IFN-γ	Interferon gamma
IL	Interleukin
IM	Intramuscular
IMT	Immunomodulatory therapy

Abbreviation or special term	Explanation
INR	International normalized ratio
IP	Investigational product
irAE	Immune-related adverse events
irRECIST	Immune-related response criteria updated with RECIST 1.1
ISH	In situ hybridization
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver function test
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
MDSC	Myeloid-derived suppressor cell
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Prothrombin time
q12w	Every 12 weeks
q2w	Every 2 weeks

Abbreviation or special term	Explanation
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QC	Quality check
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	Ribonucleic acid
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
sPD-L1	Soluble programmed cell death ligand 1
TIL	Tumor-infiltrating lymphocytes
TMG	Toxicity Management Guideline
TNBC	Triple-negative breast cancer
TSH	Thyroid-stimulating hormone
UBC	Urothelial bladder cancer
ULN	Upper limit of normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Cancer and immune function

The connection between cancer and the immune system was first uncovered nearly 100 years ago, long before an in-depth knowledge of the intricate workings of the immune system existed (Cancer Research Institute 2003). Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immunocompetent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggest that this may be an oversimplification. Some sporadic tumors are highly immunogenic but actively suppress the local immune environment through production of immunosuppressive cytokines (Shields et al 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity.

The complexity and redundancy of the immune system offer multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. Immune response may be augmented by direct stimulation of effector cells; increased antigen presentation leading to indirect stimulation of effector cells or co-stimulation; or by suppressing immunosuppressive factors, cells, or transcription (Monti et al 2005).

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers (Gooden et al 2011). Most tumors show infiltration by TILs, but tumors modulate the local micro-environment through surface expression or release of inhibitory molecules. Engagement of TIL cell surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression (Baitsch et al 2012, Crespo et al 2013). Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types (Brahmer et al 2010, Hodi et al 2010, Robert et al 2011, Topalian et al 2012, Wolchok et al 2009). Specifically, blockade of immune checkpoint signaling, through cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1), has shown clinical activity not only in conventionally immune-responsive tumors, such as melanoma and renal cell carcinoma, but also in non-small cell lung cancer (NSCLC; Brahmer et al 2010, Brahmer et al 2012, Gordon et al 2013, Topalian et al 2012), prostate cancer (Harzstark and Small 2010, Slovin et al 2013), mesothelioma (Calabrò et al 2013), and other solid tumors (Brahmer et al 2010, Brahmer et al 2012, Gordon et al 2013).

1.1.2 Tremelimumab

Tremelimumab, a CTLA-4 mAb of the immunoglobulin G (IgG) 2 kappa isotype, is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca;

AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to B7, leading to indirect prolongation and enhancement of T-cell activation and expansion.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab, both as monotherapy and combination therapy with conventional anticancer agents, to support various cancer indications using different dose schedules. As of the data cut-off date of 12 November 2014 (for all studies except Study D4190C00006, which has a cut-off date of 4 December 2014), 973 patients have received tremelimumab monotherapy (not including 497 patients who have been treated in the blinded Phase IIb study, D4880C00003) and 208 patients have received tremelimumab in combination with other agents. More than 800 of these patients had melanoma and were treated at a dose of 15 mg/kg every 90 days. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.1. Refer to the tremelimumab Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information; see Section 6.8 for guidance on management of tremelimumab-related toxicities.

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

1.1.3 MEDI4736

MEDI4736 is a human mAb of the IgG 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca for use in the treatment of cancer. The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1, expressed on cancer cells and a subset of leukocytes, with the PD-1 (cluster of differentiation [CD] 279) and B7-1 (CD80) molecules on antigen-presenting cells and T cells. By binding to PD-L1 on tumor cells, the mechanism of action of MEDI4736 includes stimulation of the patient's antitumor immune response.

MEDI4736 has been given to humans as monotherapy or in combination with other drugs as part of ongoing studies. As of 14 July 2014, 509 patients have been enrolled and treated in 10 ongoing clinical studies on MEDI4736 (with 5 studies using MEDI4736 as monotherapy and 5 studies using MEDI4736 as combination therapy). No studies have yet been completed. Details on the safety profile of MEDI4736 monotherapy are summarized in Section 1.3.2.2. Refer to the MEDI4736 IB for a complete summary of non-clinical and clinical information; see Section 6.8 for guidance on management of MEDI4736-related toxicities.

MEDI4736 monotherapy exhibits non-linear (dose-dependent) PK approaching linearity with the ≥3-mg/kg dose, likely due to saturable target-mediated clearance, and has a half-life of approximately 21 days. As of 14 July 2014, of the 220 patients who received MEDI4736 monotherapy for whom PK/ADA data were available from Study CD- ON-MEDI4736-1108 (referred to hereafter as Study 1108), 5 patients (1 patient each in the 0.1- and 3-mg/kg dose cohorts and 3 patients in 10-mg/kg dose cohort) were detected to be ADA positive, with an impact on PK/pharmacodynamics in 1 patient in the 3-mg/kg dose cohort.

1.1.4 MEDI4736 in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012) because the mechanisms of action of CTLA-4 and PD-1 are non-redundant; therefore, AstraZeneca is also investigating the use of MEDI4736 + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/pharmacodynamics, and preliminary antitumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is MEDI4736 every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses, then tremelimumab every 12 weeks (q12w) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

As of 15 April 2015, a total of 102 patients have been treated in the study, including 74 patients on the q4w dosing schedule and 28 patients on the q2w dosing schedule. Details on the safety profile of the MEDI4736 + tremelimumab combination therapy are summarized in Sections 1.2.2.3 and 1.3.2.3. Refer to the current MEDI4736 IB and tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.8 for guidance on management of MEDI4736 + tremelimumab combination therapy-related toxicities.

As of 27 January 2015 in Study D4190C00006, an approximately dose-proportional increase in PK exposure (maximum plasma concentration [C_{max}], trough plasma concentration [C_{trough}], and area under the plasma drug concentration-time curve from time 0 to Day 28 post-dose [$AUC_{(0\text{-}28)day}$]) of both MEDI4736 and tremelimumab was observed over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w and 1 to 10 mg/kg tremelimumab q4w. Four of 60 patients were ADA positive for either anti-MEDI4736 or anti-tremelimumab antibodies post-treatment; MEDI4736 PK was impacted in only 2 of these 4 patients. Complete soluble PD L1 (sPD-L1) suppression (surrogate for PD-L1 targeting) was observed in almost all patients over the dose range of 3 to 20 mg/kg of MEDI4736 q4w or q2w.

1.1.5 Rationale for conducting this study

Tremelimumab, an anti-CTLA-4-targeting agent that blocks the interaction with CD80 and CD86, may help prolong and enhance T-cell activation and expansion. This hypothesis is supported by emerging clinical data from both tremelimumab studies (Kirkwood et al 2010, Ribas et al 2013) and studies with a related anti-CTLA-4 antibody, ipilimumab. Responses with CTLA-4-targeted drugs have been documented across a variety of tumor types.

MEDI4736, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of antitumor T cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile (Brahmer et al 2012, Topalian et al 2012). In addition, although clinical experience with MEDI4736 is limited, currently available data

from Study 1108 indicate encouraging response rates and duration of response (DoR) with a manageable safety profile in patients with a variety of solid tumors.

Based on the preliminary clinical efficacy and safety data observed in patients with solid tumors who received MEDI4736 in Study 1108 and MEDI4736 + tremelimumab combination therapy in Study D4190C00006, the Sponsor plans a comprehensive development program of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy in select advanced solid tumor indications. The objectives of this program are to determine the activity of MEDI4736 as monotherapy in patients with select advanced solid tumors and to establish the role of MEDI4736 in combination with tremelimumab and other investigational agents and therapies in patients with these select advanced solid tumors. As tremelimumab monotherapy has not previously been investigated in a population of patients with many of these tumor types, the objective of this clinical trial is to determine the activity of tremelimumab as monotherapy in patients with these tumors and to determine the efficacy and safety of sequenced MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after confirmed progression on tremelimumab monotherapy or during follow-up. To our knowledge, there are limited data on the efficacy of MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after failure of tremelimumab monotherapy in the selected tumor types. In melanoma, responses with PD 1/PD-L1-targeted drugs occur after progression on anti-CTLA-4 therapy (Weber et al 2015). PD-1-based therapy has been shown to have a unique T-cell gene expression pattern when compared to CTLA-4, with minor overlap. The sequential administration of anti-CTLA-4 and anti PD 1 therapies led to increased T-cell gene expression (Das et al 2015).

These rationales support the proposed investigation of tremelimumab monotherapy with subsequent treatment with either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy in eligible patients in a single-arm Phase II setting in select advanced solid tumors as outlined in this Clinical Study Protocol (CSP). (Additional tumor types may be added at the discretion of the Sponsor.) Data generated from this study may also be used to demonstrate the contribution of components from a novel drug combination (tremelimumab and MEDI4736) with regard to other studies (ie, objective response rate [ORR], progression-free survival [PFS]).

1.2 Rationale for study design, doses and control groups

1.2.1 Tumor type selection rationale

This study will be conducted in adult patients (aged ≥18 years) with advanced and metastatic solid tumors including but not limited to histologically or cytologically documented urothelial bladder cancer (UBC), pancreatic ductal adenocarcinoma (PDAC), or triple-negative breast cancer (TNBC) (see Section 3.1). Additional tumor types may be added at the discretion of the Sponsor.

There remains a significant unmet medical need for additional treatment options for patients with UBC who have failed first-line platinum-based (ie, cisplatin or carboplatin) chemotherapy in the metastatic setting. To date, no standard therapy has been established for

patients who recur or are refractory to first-line therapy (NCCN Bladder Cancer Guidelines Version 2.2014). Several lines of evidence documenting the immune dysfunction associated with bladder cancer support the hypothesis that immunotherapy can alter the process of carcinogenesis (Carneiro et al 2014).

A study treating patients with localized UBC and with a brief exposure to ipilimumab, an anti CTLA-4 antibody, prior to surgery was associated with an increased frequency of $CD4+ICOS^{hi}$ T cells in the systemic circulation and bladder tissue. The same study analyzed a subset cohort of patients with metastatic melanoma and demonstrated that increased frequency of $CD4+ICOS^{hi}$ T cells sustained over a period of 12 weeks correlated with an increased likelihood of overall survival (OS) (Carthon et al 2010). Additionally, a study involving MPDL3280A, an anti-PD-L1 antibody, reported 30 of the 87 patients with UBC, who progressed following platinum-based first-line therapy, had responses, including 9 with complete response (CR) and 21 with partial response (PR) in patients (Petrylak et al 2015).

A significant unmet medical need also exists for additional treatment options for patients with advanced pancreatic cancer who have failed 5-fluorouracil (FU)-containing or gemcitabine-containing first-line chemotherapy. Several lines of evidence documenting the immune dysfunction associated with PDAC support the hypothesis that immunotherapy can alter the process of carcinogenesis (Fokas et al 2014). Treatment with single agent ipilimumab at a dose of 3 mg/kg demonstrated a significant delayed response in 1 patient, suggesting that immunotherapy may have an effect in PDAC (Royal et al 2010). Furthermore, the combination of anti-PD-L1 mAb and gemcitabine exhibited a significant synergistic effect on murine pancreatic cancer and resulted in CR without overt toxicity (Nomi et al 2007). Other studies have demonstrated that clinical responses to immunotherapy in PDAC may require prolonged treatments (Dung et al 2013).

Additionally, there remains a significant unmet medical need for additional treatment options for patients with triple-negative breast cancer who have failed chemotherapy. Several lines of evidence documenting the immune dysfunction associated with triple-negative breast cancer support the hypothesis that immunotherapy can alter the process of carcinogenesis. TILs can provide prognostic and potentially predictive value in triple-negative breast cancer (Salgado et al 2015, Loi et al 2014). TILs may be associated with responses to chemotherapy (Perez et al 2014). In KEYNOTE-012, 5 of 27 patients with TNBC had a response to Pembrolizumab, a PD-1 antibody, including 1 CR. An additional 7 patients had stable disease (SD; 25.9%). Only patients with PD-L1-positive tumors (PD-L1 stromal staining or >1% of tumor cells) were enrolled (Nanda et al 2014). In a Phase Ia study with MPDL-3280A, a PD-L1 antibody, 3 of 9 patients with TNBC had a response. Only patients with PD-L1-positive tumors were enrolled (PD-L1 positivity was assessed on TILs using immunohistochemistry (IHC); IHC 2/3 were considered positive [>10% TILs or 5% to 10% TILs]; Emens et al 2014).

1.2.2 Dose rationale

1.2.2.1 Tremelimumab monotherapy dose rationale

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer

agents to support various cancer indications using different dose schedules. A total of 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Tremelimumab has been administered as a single-agent treatment in 10 of these clinical studies, 2 of which continue to follow patients. In total, 973 patients with a variety of tumor types have been treated in these studies (not including an ongoing Phase IIb study [Study D4880C00003] in patients with mesothelioma). In addition, tremelimumab in combination with other anticancer agents has been administered to 208 patients with a variety of tumor types in 12 of the 22 clinical studies, 7 of which are ongoing.

Across the clinical development program for tremelimumab and that of the related anti-CTLA-4 antibody ipilimumab, a pattern of efficacy and safety has emerged that appears to be consistent across different tumor types for anti-CTLA-4 agents. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%; however, in patients who respond, the responses are often durable, lasting several months even in patients with aggressive tumors, such as refractory metastatic melanoma. The profile of adverse events (AEs) and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with that of other CTLA-4 antibodies. Additional details on AEs are available in the tremelimumab IB.

The target trough concentration of tremelimumab is estimated to be approximately 30 µg/mL, based on enhanced interleukin (IL)-2 release (in vitro) and antitumor activity (in vivo) in preclinical studies. PK simulations indicate that, following a dose of 10 mg/kg q4w for 6 months, approximately 90% of patients are expected to be above this target level of 30 µg/mL during the induction phase. Tremelimumab at a dose of 10 mg/kg q4w for 6 months followed by 10 mg/kg every 90 days is expected to yield PK exposures similar to those of the related anti-CTLA-4 mAb ipilimumab, given at a dose of 10 mg/kg every 3 weeks (q3w) for 4 cycles (12 weeks) followed by 10 mg/kg every 3 months (beginning on Week 24), the dosing regimen that was tested in the pivotal first-line melanoma trial (Robert et al 2011).

Retrospective analyses of the Phase I and II tremelimumab melanoma studies show an improvement in OS for patients who were able to achieve a higher tremelimumab exposure, as measured by the area under the plasma drug concentration-time curve (AUC). The median OS was significantly longer in the high-AUC group (15.3 months; N=164) versus the low-AUC group (6.0 months; N=163) (based on the median value of AUC [103570 µg•h/mL]). This difference in OS corresponds to a hazard ratio (HR) of 0.41 ($p<0.001$), and the estimated survival rates in these 2 groups were 59% versus 29%, respectively, at 1 year. Additionally, a retrospective exposure and survival analysis of 293 patients treated with tremelimumab in a Phase III study in patients with melanoma showed better OS in patients with higher exposure. The median OS was 18.4 months for the high-AUC group (≥123665 µg•h/mL) compared to 9.0 months for the low-AUC group (<123665 µg•h/mL) (HR 0.5; $p<0.001$). Tremelimumab monotherapy at a dose of 750 mg q4w for 7 doses (cycles) followed by 750 mg q12w for 2 additional doses (cycles) is equivalent to 10 mg/kg tremelimumab monotherapy with the same dosing schedule. Therefore, the current study will use a dosing regimen of 750 mg q4w for 7 doses followed by 750 mg q12w for 2 doses to maximize exposure to tremelimumab while managing safety according to established guidelines.

As of DCO date (12 July 2017), approximately 1617 patients have been exposed to one or more doses of tremelimumab monotherapy across the program (see tremelimumab IB version 8 dated 02 Nov 2017). Clinical experience has not resulted in material changes to the clinical AE profile or to the TMGs. Refer to updated TMGs in Appendix E.

1.2.2.2 MEDI4736 monotherapy dose rationale

A dose of MEDI4736 20 mg/kg q4w is supported by in vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors (ongoing first-time-in-humans study) and from a Phase I trial performed in Japanese patients with solid tumors (NCT01938612).

Pharmacokinetic/pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg q3w, MEDI4736 exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the MEDI4736 dosing frequency can be adapted to a particular regimen, given the linearity seen at higher doses than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of MEDI4736 with PD-L1. Dose-related changes in a variety of peripheral biomarkers have been observed over the dose range of 0.1 to 15 mg/kg. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to MEDI4736. Of the 220 patients who received MEDI4736 monotherapy and for whom PK/ADA data were available as of 14 July 2014, 5 patients were ADA positive, with an impact on PK/pharmacodynamics reported in 1 patient at the 3-mg/kg dose range.

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of MEDI4736 and tremelimumab) also show an approximately dose-proportional increase in PK exposure for MEDI4736 over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w. (For further information on PK observations in Study D4190C00006, please refer to Section 1.2.2.3).

The observed MEDI4736 PK data from the combination study were well in line with the predicted monotherapy PK data (5^{th}, median, and 95^{th} percentiles) for a q4w regimen. (For further information on PK observations in Study D4190C00006, please refer to Section 1.2.2.3).

A population PK model was developed using the data from Study 1108 (doses of 0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUC at steady state (AUC_{ss}; 4 weeks). Median C_{max} at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median C_{trough} at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg

q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar AUC and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.

Clinical data

As of 8 April 2015, there is initial safety data for 16 patients receiving the 20 mg/kg q4w dosing regimen (12 patients from Study 1108 and 4 patients from the Japan Phase I trial). The toxicities observed with 20 mg/kg q4w are consistent with the 10 mg/kg q2w regimen, and there were no dose-limiting toxicities (DLTs) observed. Of the 12 patients in Study 1108, 42% of patients have experienced AEs of any grade, with 2 being Grade 3 and above (17%). None of the Grade 3 and higher AEs were considered treatment related. No patients on the Japan Phase I trial have experienced an AE Grade 3 or above. At present, the data do not suggest that the safety profile of MEDI4736 will be different in the 20 mg/kg q4w dosing regimen when compared to 10 mg/kg q2w dosing regimen. As of 14 July 2014, 393 patients enrolled in Study 1108 have received MEDI4736, predominantly at 10 mg/kg q2w (either in the dose-escalation or dose-expansion phase of the study). Data presented at the European Society for Medical Oncology (ESMO) meeting 2014 with a later cutoff date of 21 August 2014 showed that MEDI4736 was well tolerated at all doses in the subset of patients with NSCLC enrolled into Study 1108, with drug-related Grade ≥3 AEs reported in 3% of patients and drug-related AEs leading to discontinuation reported in 1% of patients. No drug-related colitis or hyperglycemia of any grade, Grade ≥3 pneumonitis, or drug-related AEs leading to death were reported (Antonia et al 2014). No DLTs were observed up to a dose of 10 mg/kg q2w or 15 mg/kg q3w.

Efficacy data on the patients with NSCLC in Study 1108, presented at ESMO 2014 (cutoff date of 21 August 2014), showed a disease control rate (DCR) at 12 weeks of 41% and an ORR of 16% among 162 evaluable patients, with activity observed in both squamous and non-squamous histologies. The ORR was higher (25%; 12 CR/PR; n=48) in patients with PD-L1 positive tumors, defined as those with ≥25% of tumor cells with membrane staining for PD-L1, compared to patients with PD-L1-negative tumors (10%; 7 CR/PR; n=74) (Antonia et al 2014).

As of the DCO date (12 July 2017), across the entire clinical development program, an estimated 4067 patients have been exposed to 1 or more doses of durvalumab in Phase I to III studies, either as monotherapy or in combination, and 5911 patients where the treatment arm is blinded. Additionally, approximately 4000 patients have been exposed to 1 or more doses of durvalumab in ESR/IITs (see Appendix B Table 46 in MEDI4736 IB version 12 dated 03 Nov

2017). Estimates of overall cumulative patient exposure based on actual exposure data from any completed clinical trials and the enrolment/randomisation schemes for ongoing open label and blinded trials are: 3723 patients received durvalumab monotherapy, 3372 patients received durvalumab in combination with tremelimumab. The total post-marketing exposure to durvalumab from May 2017 to the 12 July 2017 was estimated to be approximately 1.46 patient-years. Clinical experience has not resulted in material changes to the clinical AE profile or to the TMGs. Refer to updated TMGs in Appendix E.

1.2.2.3 MEDI4736 + tremelimumab combination therapy dose rationale

The MEDI4736 + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of MEDI4736 and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetic/pharmacodynamic data

In order to reduce the dosing frequency of MEDI4736 to align with the q4w dosing of tremelimumab while ensuring an acceptable PK/pharmacodynamics, safety, and efficacy profile, cohorts in Study D4190C00006 were narrowed to 15 and 20 mg/kg MEDI4736 q4w. PK simulations from the MEDI4736 monotherapy data indicated that a similar AUC_{ss} (4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w MEDI4736. The observed MEDI4736 PK data from Study D4190C00006 were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of MEDI4736 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when MEDI4736 and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with MEDI4736 monotherapy. There was evidence of augmented pharmacodynamic activity relative to MEDI4736 monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab combinations.

Clinical data

As of 15 April 2015, a total of 102 patients with advanced NSCLC have been treated in Study D4190C00006. Various dose combinations were explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of MEDI4736 ranging from 3 to 20 mg/kg. A total of 74 of these patients were in the q4w dosing schedule, and 28 patients were in the q2w dosing schedule, with the goal of identifying the dose combination that best optimizes the benefit: risk profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher incidence of AEs, including Grade 3 or 4 AEs, discontinuations due to AEs, and serious AEs (SAEs). Between

the 10-mg/kg MEDI4736 + 1-mg/kg tremelimumab and 10-mg/kg MEDI4736 + 3-mg/kg tremelimumab dose cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10-mg/kg MEDI4736 + 3-mg/kg tremelimumab dose cohort than in the 10-mg/kg MEDI4736 + 1-mg/kg tremelimumab dose cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis, and colitis were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the cohorts using 1-mg/kg of tremelimumab. Together, these data suggest that tremelimumab at a dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with MEDI4736. As a result, all combination doses utilizing either the 3- or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of MEDI4736 with a constant dose of tremelimumab did not show an increase in the incidence of AEs. The data suggested that increasing doses of MEDI4736 may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10- and 20-mg/kg dose cohorts were similar, with a similar safety profile observed between the 10- and 20-mg/kg dose cohorts.

In Study D4190C00006, of all treatment cohorts, the cohort of 18 patients treated in the 20 mg/kg MEDI4736 q4w + 1 mg/kg tremelimumab group had the lowest incidence of AEs and treatment discontinuations due to AEs, second lowest incidence of any Grade ≥3 AEs, and third lowest incidence of SAEs, but still showed strong evidence of clinical activity. This cohort had a lower percentage of treatment-related Grade ≥3 AEs or AEs leading to discontinuation.

Preliminary clinical activity of the MEDI4736 + tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 10-, 15-, and 20-mg/kg MEDI4736 q4w dose cohorts at all doses of tremelimumab and the 10-mg/kg MEDI4726 q2w + 3-mg/kg tremelimumab dose cohort demonstrated objective responses.

Efficacy data suggested that the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. All 8 patients in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort were evaluable for efficacy with at least 16 weeks of follow-up. Of these, there were 4 patients (50%) with ORR and 4 patients (50%) with durable clinical response (CR, PR, or SD).

Additionally, of all cohorts, the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. All together, the data suggested that a 20 mg/kg (approximately 1.5 g) MEDI4736 + 1 mg/kg (approximately 75 mg) tremelimumab dose combination should be selected for further development.

As of the DCO date (12 July 2017), across the entire clinical development program, an estimated 4067 patients have been exposed to 1 or more doses of durvalumab in Phase I to III studies, either as monotherapy or in combination, and 5911 patients where the treatment arm

is blinded. Additionally, approximately 4000 patients have been exposed to 1 or more doses of durvalumab in ESR/IITs (see Appendix B Table 46 in MEDI4736 IB version 12 dated 03 Nov 2017). Estimates of overall cumulative patient exposure based on actual exposure data from any completed clinical trials and the enrolment/randomisation schemes for ongoing open label and blinded trials are: 3723 patients received durvalumab monotherapy, 3372 patients received durvalumab in combination with tremelimumab. The total post-marketing exposure to durvalumab from May 2017 to the 12 July 2017 was estimated to be approximately 1.46 patient-years. Clinical experience has not resulted in material changes to the clinical AE profile or to the TMGs. Refer to updated TMGs in Appendix E.

1.2.2.4 Rationale for 4 cycles of combination therapy followed by MEDI4736 monotherapy

Long-term follow-up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed q3w for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow-up (Schadendorf et al 2013).

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

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

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

Similar long term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1 antibodies such as MEDI4736, or the MEDI4736 + tremelimumab combination.

The MEDI4736 + tremelimumab combination therapy regimen will be administered for 4 cycles followed by monotherapy MEDI4736 1.5 g q4w.

1.2.2.5 Rationale for fixed dosing

A population PK model was developed for MEDI4736 using monotherapy data from Study 1108 (Phase I study; N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors).

Population PK analysis indicated only a minor impact of body weight on the PK of MEDI4736 (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) regimens of MEDI4736 was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on a median body weight of approximately 75 kg). A total of 1000 patients were simulated using a body weight distribution of 40 to 120 kg. Simulation results demonstrated that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with the fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III studies (N=654; doses=0.01 to 15 mg/kg q4w or every 90 days; metastatic melanoma; Wang et al 2014). A population PK model indicated minor impact of body weight on the PK of tremelimumab (coefficient of ≤0.5). The body weight-based (1 mg/kg q4w) and fixed dosing (75 mg/kg q4w; based on a median body weight of approximately 75 kg) regimens of tremelimumab were compared using predicted PK concentrations (5th, median, and 95th percentiles) using a population PK model in a simulated population of 1000 patients with a body weight distribution of 40 to 120 kg. Similar to MEDI4736, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less overall between-patient variability with the fixed dosing regimen.

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

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 1.5 g q4w MEDI4736 (equivalent to 20 mg/kg q4w) and 75 mg q4w tremelimumab (equivalent to 1 mg/kg q4w) as well as 750 mg tremelimumab (equivalent to 10 mg/kg) is included in the current study.

1.2.3 Rationale for retreatment options

In contrast to patients treated with chemotherapy, who are unlikely to respond to rechallenge with the same agent upon progression, responses have been observed upon retreatment with IMTs. Several potential mechanisms of resistance to IMT exist, including loss of T-cell "memory" or recurrence of immune escape, which suggest that retreatment for patients who initially respond or demonstrate SD is reasonable. Preliminary data in patients previously treated with IMTs suggest that responses are similar to those observed following initial treatment (Forde et al 2015; Hodi et al 2010). Therefore, patients receiving tremelimumab

monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy who achieve and maintain disease control (ie, CR, PR, or SD) through the end of the 12-month treatment period may restart treatment with their assigned treatment upon evidence of progressive disease (PD) during follow-up. In addition, patients receiving combination therapy who complete the 4 dosing cycles with the combination of MEDI4736 + tremelimumab (with clinical benefit per Investigator judgment), but subsequently experience progression (according to Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1]) during treatment with MEDI4736 alone, will be given the option to restart MEDI4736 + tremelimumab combination therapy. All patients who restart treatment will receive a maximum of 12 months of further treatment. For details on the retreatment criteria for this study, see Section 7.2.2.

1.2.4 Rationale for sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after confirmed disease progression

The rationale for providing an option to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after confirmed disease progression during treatment with tremelimumab monotherapy or during follow-up is supported by both non-clinical and clinical data. Non-clinical evidence shows that anti-CTLA-4-based therapy upregulates PD-L1 expression (Wolchok et al 2013). Additionally, recent data have demonstrated that combination blockade of CTLA-4 and PD-1 leads to distinct biological changes that are not observed with blockade of each checkpoint alone (Das et al 2015). Clinical data demonstrate efficacy with anti-PD-1-based therapy after progression on anti-CTLA-4 (ipilimumab; Robert et al 2014, Wolchok et al 2013). Also, sequential therapy with anti-CTLA-4 and anti-PD-1 agents has shown promising activity in patients with melanoma, with 70% of patients alive at 1 year and 31% of patients with a >80% reduction in tumor burden with sequential therapy at 36 weeks (Sznol et al 2014). For details on the sequencing criteria for this study, see Section 7.2.3.

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy prior to the overall benefit-risk assessment.

1.3.1 Potential benefits

1.3.1.1 Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, a response rate of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis; Korn et al 2008) were observed (Kirkwood et al 2010). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed a response rate of 11% and a median OS of 12.58 months in this first-line setting as compared

to 10.71 months with standard chemotherapy; however, these results were not statistically significant (Ribas et al 2013). Additionally, in a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who have responded or remained stable, PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

1.3.1.2 MEDI4736

Of the 414 patients treated with MEDI4736 (all dose levels) in all tumor types in Study 1108 as of 14 July 2014, a total of 169 patients were evaluable for response analysis, which included patients who had at least 24 weeks of follow-up as of 14 July 2014 and had either at least 1 post-baseline tumor assessment or experienced clinical PD or death. Nineteen patients (11.2%) had a best overall response of confirmed and unconfirmed CR/PR. The DCR (CR + PR + SD ≥12 weeks) was 32% (54 of 169 patients). PD-L1 status (based on Ventana/MedImmune assay) was known for 143 of 169 evaluable patients, of whom 30 had PD-L1-positive tumors (defined by tumor staining >25%). A best overall response of CR/PR (confirmed and unconfirmed) was observed in 7 of 30 patients (23.3%) with PD-L1-positive tumors and in 6 of 113 patients (5.3%) with PD-L1-negative tumors.

1.3.1.3 MEDI4736 + tremelimumab

The non-clinical and clinical justification for this combination as noted in Section 1.2.2.3 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma (Wolchok et al 2013). Furthermore, preliminary efficacy data from Study D4190C00006 have demonstrated that this combination is clinically active and well tolerated. As of 15 April 2015, 63 patients were evaluable for response across various MEDI4736 + tremelimumab combination therapy dose regimens. In the MEDI4736 20-mg/kg plus tremelimumab 1-mg/kg q4w dose cohort, a total of 8 of 18 patients were evaluable for efficacy with at least 16 weeks of follow-up.

1.3.2 Potential risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects, can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and

liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

1.3.2.1 Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia.

For information on all identified and potential risks with tremelimumab please always refer to the current version of the tremelimumab IB.

1.3.2.2 MEDI4736

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

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 (please see Appendix E).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.3.2.3 MEDI4736 + tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20m/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab+tremelimumab combination please always refer to the current version of the durvalumab IB

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, diarrhoea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, oedema peripheral, weight, decreased hyponatraemia and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

1.3.3 Overall benefit and risk assessment

There remains a significant unmet medical need for additional treatment options for patients with advanced solid tumors. Responses to currently available chemotherapies and targeted therapies offer little in terms of durable response, and many have significant toxicities that affect a patient's perceived quality of life (QoL). Treatment with agents targeting CTLA-4 or PD-1/PD-L1 has shown activity in several tumor types, with a subset of patients deriving meaningful and durable benefit. Across the clinical development program for tremelimumab, a pattern of efficacy has emerged that is similar to that of the related anti-CTLA-4 antibody, ipilimumab. The efficacy of tremelimumab appears to be consistent across tumor types. Thus, tremelimumab may potentially offer benefit to this patient population. The study design aims to minimize potential risks, and intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with IPs.

The toxicity profile of tremelimumab includes diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, headache, pyrexia, abdominal pain, and colitis. The toxicity profile of MEDI4736 includes fatigue, nausea, diarrhea, decreased appetite, rash, vomiting, pruritus, dyspnea, pyrexia, hypothyroidism, increased ALT, increased AST, cough, myalgia, abdominal pain, and dizziness.

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, the activity seen with tremelimumab across tumor types, and the strength of the scientific hypotheses under evaluation, the tremelimumab monotherapy with potential sequencing, after confirmed progression during treatment or follow-up, to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy proposed for evaluation in this study may have the ability to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable clinical responses, thereby improving QoL and potentially extending survival. The overall benefit: risk assessment is appropriate per the proposed study design.

1.4 Study Design

This is an open-label, multi-center study to determine the efficacy and safety of tremelimumab monotherapy (750 mg via intravenous [IV] infusion q4w for 7 doses [cycles], then q12w for 2 additional doses [cycles] for up to a total of 12 months [9 doses (cycles) total]) in the treatment of different patient cohorts with specified advanced solid tumors. (Additional tumor types may be added at the discretion of the Sponsor.) If eligible and at the discretion of the Investigator, after confirmed disease progression on tremelimumab monotherapy or during follow-up, patients will also have the option of being sequenced to MEDI4736 monotherapy (1.5 g via IV infusion q4w for up to a total of 12 months [13 doses (cycles)]) or MEDI4736 + tremelimumab combination therapy (MEDI4736 1.5 g via IV infusion q4w in combination with tremelimumab 75 mg via IV infusion q4w for up to 4 cycles each, followed by MEDI4736 1.5 g via IV infusion q4w for up to a total of 8 months [9 additional doses (cycles)]), for up to 12 months or until disease progression, whichever comes sooner.

Schematic diagrams of the overall study design are shown in Figure 1, Figure 2, and Figure 3, and a flowchart of the study is presented in Figure 4.

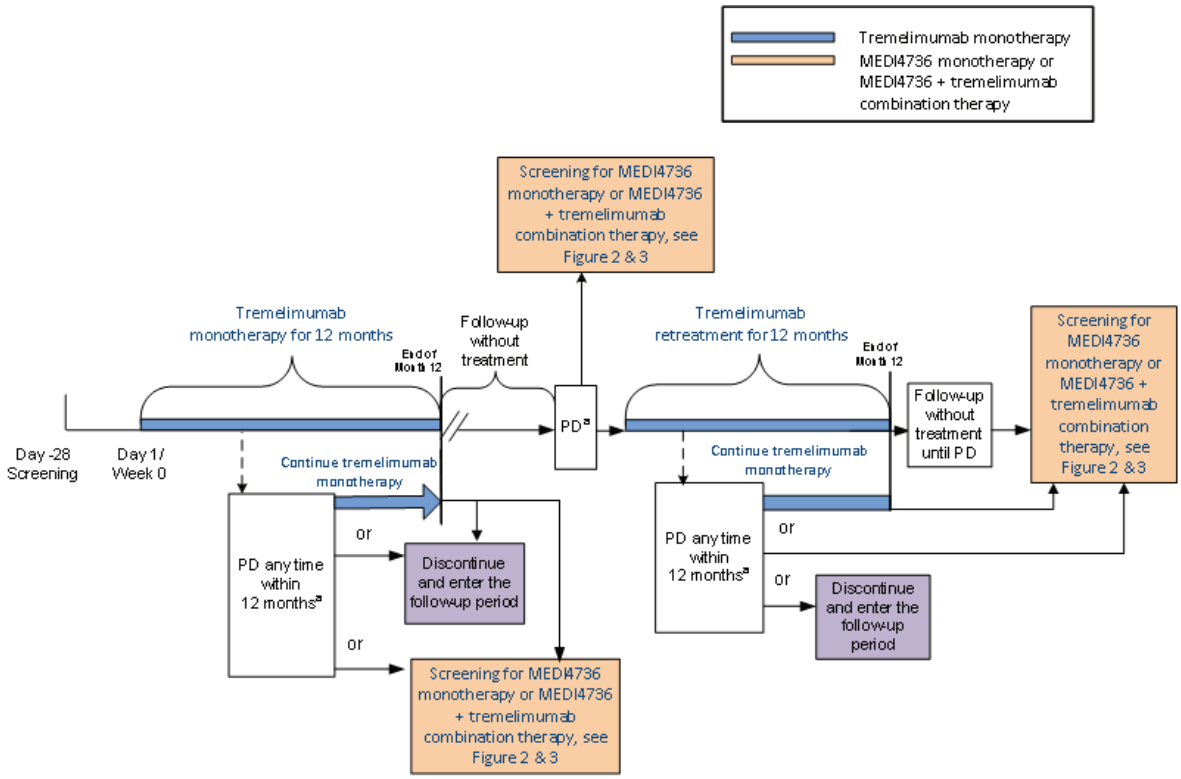
This study will screen approximately 38 patients with each selected advanced solid tumor type in order to enroll approximately 32 evaluable patients with each tumor type globally.

For each tumor cohort, a minimax Simon 2-Stage design will be used to stop recruitment early if no response is observed and thus reduce patient exposure to non-active treatment. (Ongoing patients will still be eligible to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy as previously described.) If 1 or more responses are observed in the first 20 treated patients with the selected tumor type, an additional 12 patients will be enrolled, for a total of 32 evaluable patients. If no responses are observed, the DCR data will also be evaluated to make a final decision before discontinuing the tumor cohort. If at least 10 out of the first 20 patients achieve DCR (≥50% DCR), then an additional 12

patients may be enrolled, for a total of 32 evaluable patients. Patients' tumor response and DCR will be monitored on an ongoing basis in order to minimize the time between Stage 1 and Stage 2. Tumoral PD-L1 expression will be monitored throughout the study so as to plan for further enrollment, and if necessary, a decision to enroll may be based on expression status.

Doses, treatment regimens, retreatment eligibility criteria, and sequencing eligibility criteria are described in Section 7.2. Assessments will be conducted as indicated in Table 2 and Table 3.

Figure 1 Overall study design for tremelimumab monotherapy

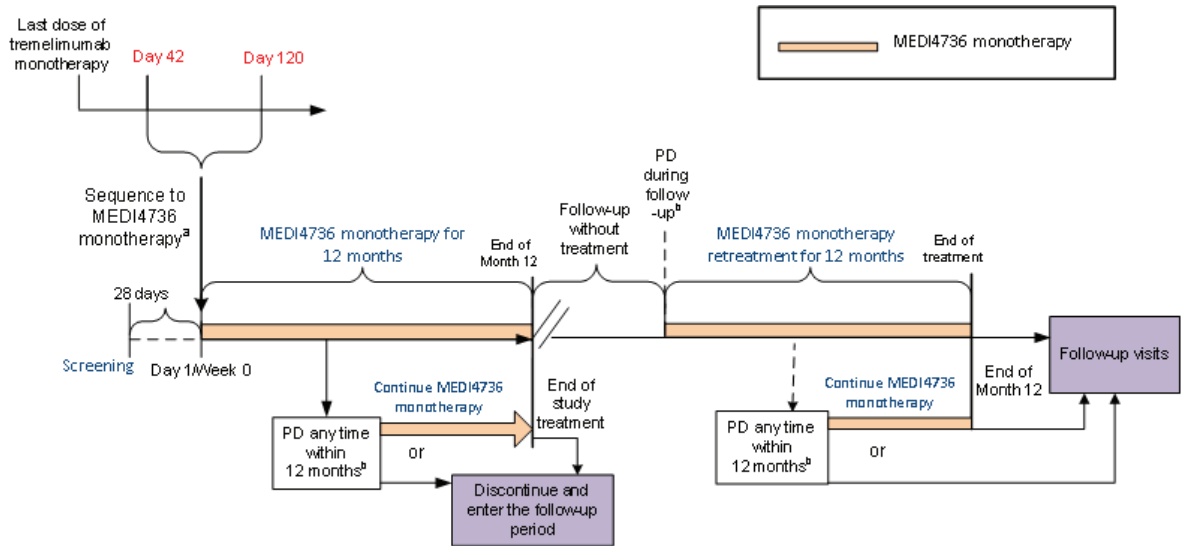


[a] PD will be according to RECIST 1.1. The decision to retreat with tremelimumab monotherapy or sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy is at the discretion of the Investigator. A confirmatory scan is required for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. In cases of unequivocal PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient before sequencing.

Note: Using a minimax Simon 2-Stage design, the first 20 evaluable patients for each tumor type will be assessed for ORR, and recruitment will be stopped early if no response is observed. (Ongoing patients will still be eligible to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy as previously described.) If 1 or more responses are observed out of the first 20 treated patients with the selected tumor type, an additional 12 patients will be enrolled, for a total of 32 evaluable patients. If no responses are observed, the DCR data will also be evaluated to make a final decision before discontinuing the tumor cohort. If at least 10 out of the first 20 patients achieve DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients may be enrolled, for a total of 32 evaluable patients. Patients' tumor response and DCR will be monitored on an ongoing basis to minimize the time between Stages 1 and 2.

Abbr: DCR Disease control rate; ORR Objective response rate; PD Progressive disease; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Figure 2 Overall study design for MEDI4736 monotherapy

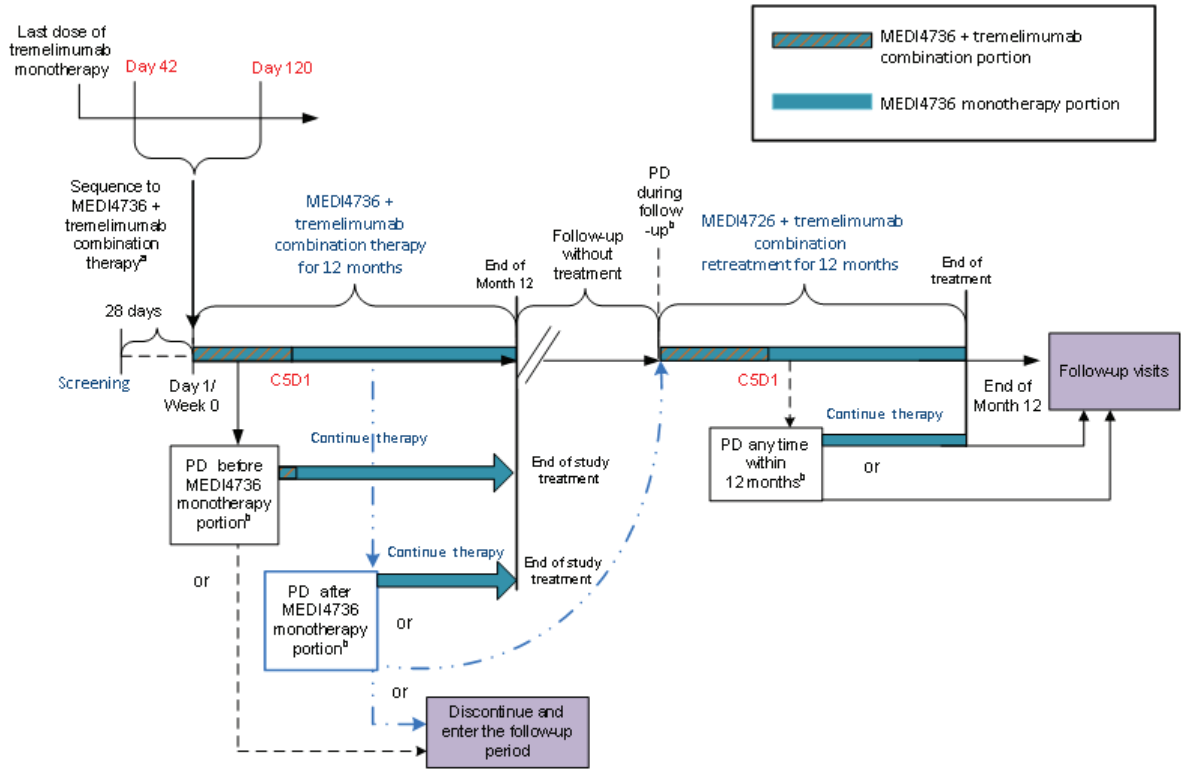


[a] For patients who have confirmed PD during the tremelimumab monotherapy follow-up period, treatment with sequenced therapy will not be more than 60 days after confirmed progression.

[b] PD will be according to RECIST 1.1. All patients who are eligible to restart treatment after screening will receive a maximum of 12 months of further treatment.

Abbr: PD Progressive disease; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Figure 3 Overall study design for MEDI4736 + tremelimumab combination therapy

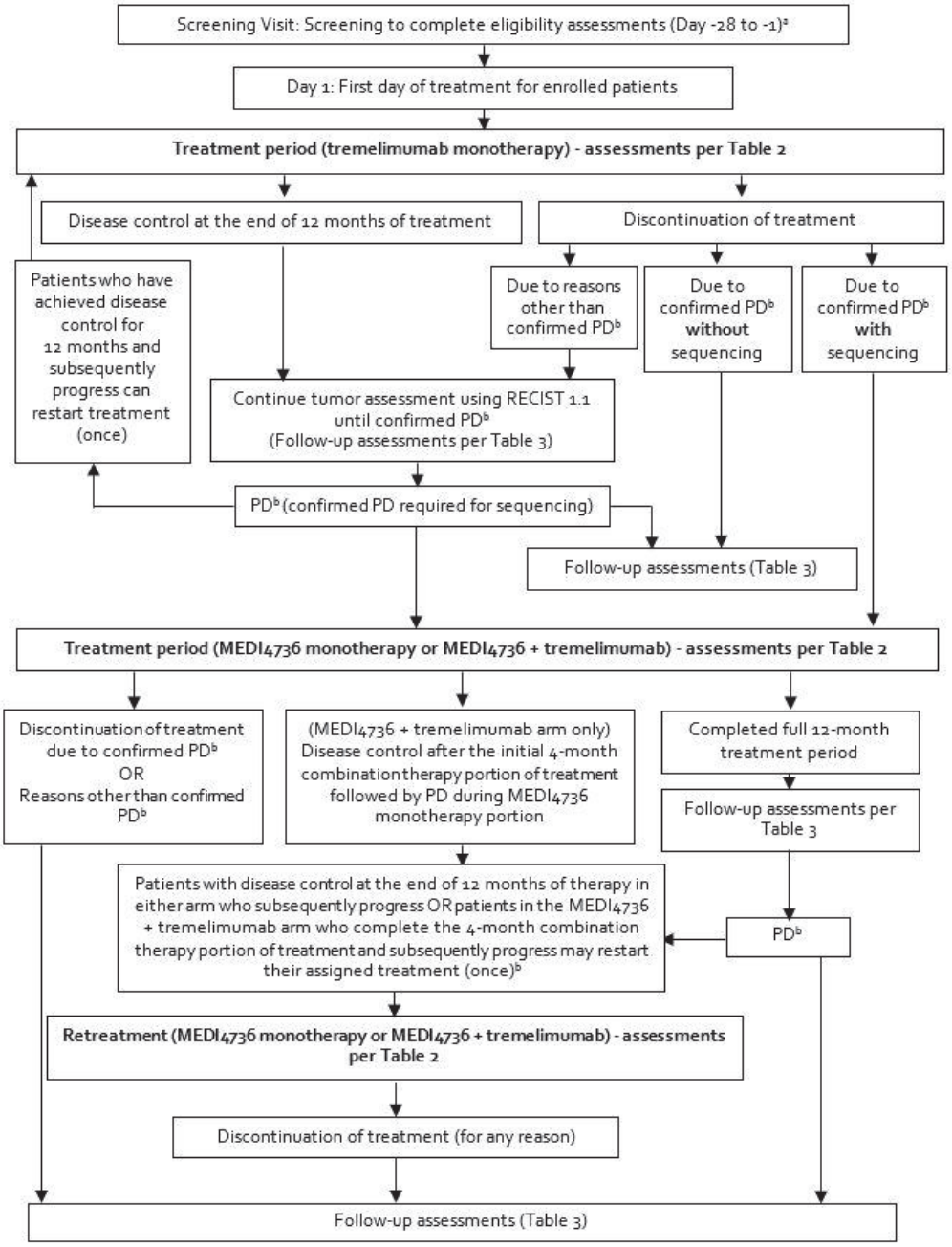


[a] For patients who have confirmed PD during the tremelimumab monotherapy follow-up period, treatment with sequenced therapy will not be more than 60 days after confirmed progression.

[b] PD will be according to RECIST 1.1. Patients receiving combination therapy who complete the 4 dosing cycles with the combination of MEDI4736 + tremelimumab (with clinical benefit per Investigator judgment), but subsequently experience progression (according to RECIST 1.1) during treatment with MEDI4736 alone, will be given the option to restart MEDI4736 + tremelimumab combination therapy (once). All patients who restart treatment will receive a maximum of 12 months of further treatment.

Abbr: PD Progressive disease; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Figure 4 Study flowchart for patients enrolled in the study



[a] Screening assessments can be performed in a step-wise process. The baseline tumor assessment should be performed within 28 days prior to enrollment. Fresh tumor biopsy samples, if necessary, should be obtained as the last step in the screening process, after the patient has been confirmed to meet all other inclusion criteria and confirmed not to meet any exclusion criteria.

[b] In addition to PR and CR, a confirmatory scan is required following the initial demonstration of PD. (See Section 5.1 for more information.) Patients must have confirmed PD on tremelimumab monotherapy or during follow-up prior to sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab

combination therapy, which is at the Investigator's discretion. In cases of unequivocal PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient before sequencing.

Abbr: CR Complete response; PD Progressive disease; PR Partial response; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of tremelimumab monotherapy in terms of ORR	ORR using Investigator assessments according to RECIST 1.1[a,b]

[a] Sensitivity analyses of ORR may be performed based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

[b] Decision to proceed to Stage 2 (ie, enroll 12 additional patients) for each tumor type will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1.

Abbr: ORR Objective response rate; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To further assess the efficacy of tremelimumab monotherapy in terms of DoR, DCR, PFS, BoR, and OS	DoR, DCR, PFS, and BoR using Investigator assessments according to RECIST 1.1[a] OS
To assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow-up in terms of ORR, DoR, DCR, PFS, BoR, and OS	ORR, DoR, DCR, PFS, and BoR using Investigator assessments according to RECIST 1.1 OS

[a] Sensitivity analyses of DoR, DCR, PFS, and BoR may be performed based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Abbr: BoR Best objective response; DCR Disease control rate; DoR Duration of response; ORR Objective response rate; OS Overall survival; PD Progressive disease; PFS Progression-free survival; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

2.3 Safety objectives

Safety Objective:	Outcome Measure:
To assess the safety and tolerability profile of tremelimumab monotherapy	AEs, physical examinations, laboratory findings, vital signs, and ECGs
To assess the safety and tolerability profile of MEDI4736 monotherapy and of MEDI4736 + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow-up	AEs and laboratory findings

Abbr: AE Adverse event; ECG Electrocardiogram; PD Progressive disease.

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To assess the PK of tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy	Concentration of tremelimumab and MEDI4736 in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow, sparse sampling)
To investigate the immunogenicity of tremelimumab and MEDI4736	Presence of ADAs for tremelimumab and MEDI4736 (confirmatory results: positive or negative)
To collect blood and tissue samples for defining biological responses to tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy and for identifying candidate markers that may correlate with likelihood of clinical benefit	Protein expression detected by IHC (eg, PD-L1) Circulating soluble factors (eg, cytokines and autoantibodies) miRNA/mRNA T-cell and MDSC phenotyping

Note: Exploratory objective analyses may be reported separately from the main Clinical Study Report.
Abbr: ADA Anti-drug antibody; IHC Immunohistochemistry; MDSC Myeloid-derived suppressor cell; miRNA Micro-ribonucleic acid; mRNA Messenger ribonucleic acid; PD-L1 Programmed cell death ligand 1; PK Pharmacokinetic(s).

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Age ≥18 years at the time of screening

2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3. Patients affected by histologically or cytologically documented solid tumor malignancies, including but not limited to 1 of the following. (Additional tumor types may be added at the discretion of the Sponsor.)

   – UBC: Second-line cohort, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1 for bladder) documented transitional cell carcinoma (transitional cell

and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra), who have failed first-line platinum-based (ie, cisplatin or carboplatin) chemotherapy in the metastatic setting are eligible. Prior surgery, localized irradiation, and/or neoadjuvant/adjuvant chemotherapy in muscle invasive disease are permitted.

- Metastatic PDAC: Second-line cohort, tumor progression following prior standard first-line 5-FU-containing or gemcitabine-containing chemotherapy. Patients cannot have received more than 1 previous chemotherapy regimen or any other systemic therapy for recurrent/metastatic PDAC. One other prior line of therapy administered either in a prior adjuvant, neoadjuvant, or definitive chemoradiation setting is permitted. (Other pancreatic malignancies [eg, acinar cell carcinomas, adenosquamous carcinomas, and neuroendocrine islet cell neoplasms] are not eligible to enroll.)

- TNBC: Second- to fifth-line cohort, after failure of 1 to 4 lines of chemotherapy in the metastatic setting. TNBC is defined as:

  - Estrogen receptor and progesterone receptor negative (not eligible for endocrine therapy) defined as IHC nuclear staining <1% AND

  - Human epidermal growth factor receptor 2 (HER-2) negative (not eligible for anti-HER-2 therapy) defined as:

    - IHC 0, 1+ without in situ hybridization (ISH) OR
    - ISH non-amplified HER-2/CEP17 ratio <2.0 and, if reported, average HER-2 copy number <4.0 signals/cells OR
    - Single-probe ISH assay average HER-2 copy numbers <4.0 signals/cells

- Are intolerant, ineligible for, or have refused treatment with standard first-line therapy for any of above mentioned recruiting solid tumor types

4. Willing to give valid written consent to provide a tumor biopsy, archival or fresh (preferred), for the purpose of establishing PD-L1 status and for exploratory biomarker analyses (see Section 5.5.1 for details)

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see section 5.3.2 for ECOG performance status)

6. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have short axis ≥15 mm) with computed tomography (CT) (preferred) or magnetic resonance imaging (MRI) scans, preferably with IV contrast, and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines. Lesions in a

previously irradiated field can be used as measurable disease provided that there has been demonstrated progression in the lesion.

7. No prior exposure to immune-mediated therapy, including but not limited to other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines.

8. Adequate organ and marrow function as defined below:

   - Hemoglobin ≥9 g/dL
   - Absolute neutrophil count ≥1500/mm^3
   - Platelet count ≥100,000/mm^3
   - Total serum bilirubin ≤1.5 × upper limit of normal (ULN); this will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia, predominantly unconjugated bilirubin, in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician
   - ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST≤5 × ULN
   - Creatinine Clearance (CrCl) ≥30 mL/min calculated by Cockcroft-Gault equation (using actual body weight; see Appendix A) or by measured 24-hour urine collection for determination of creatinine clearance. (In cases where both are performed, measured 24-hour urine collection will be used to determine eligibility)

9. Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. Or underwent surgical sterilization (bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy). The following age-specific requirements apply:

   - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
   - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses >1 year ago, had chemotherapy-induced menopause with >1-year interval since last menses.

3.2 Exclusion criteria

Patients 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/MedImmune staff and/or staff at the study site)

2. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

3. Prior randomisation or treatment in a previous MEDI4736 and/or tremelimumab clinical study regardless of treatment arm assignment.

4. Any concurrent chemotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions for palliative intent is acceptable (eg, local surgery or radiotherapy).

5. Receipt of any investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment

6. Receipt of last dose of an approved (marketed) anticancer therapy (chemotherapy, targeted therapy, biologic therapy, mAbs, etc) within 21 days prior to the first dose of study treatment. If sufficient washout time has not occurred due to the schedule or PK properties of an agent, a longer washout period will be required, as agreed upon by AstraZeneca and the Investigator.

7. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

8. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

   – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy may be included after consultation with the AstraZeneca Study Physician.

9. Current or prior use of immunosuppressive medication within 14 days before the first dose of tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

10. History of allogenic organ transplantation

11. Active or prior documented autoimmune or inflammatory disorders (including but not limited to inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis [with the exception of diverticulosis], celiac disease, systemic lupus erythematosus; Sarcoidosis syndrome, Wegener syndrome [granulomatosis with polyangiitis-Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:

    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 3 years may be included but only after consultation with AstraZeneca study physician

12. Any condition that, in the opinion of the Investigator, would interfere with evaluation of IP or interpretation of patient safety or study results, including, but not limited to, ongoing or active infection; symptomatic congestive heart failure; uncontrolled hypertension; unstable angina pectoris; cardiac arrhythmia; interstitial lung disease; serious chronic GI conditions associate with diarrhea or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from study treatment, or compromise the ability of the patient to give written informed consent.

13. Other malignancy within 5 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has been surgically cured. Cancer patients with incidental histologic findings of prostate cancer (tumor/node/metastasis stage of T1a or T1b or prostate-specific antigen <10) who have not received hormonal treatment may be included, pending a discussion with the Study Physician.

14. History of leptomeningeal carcinomatosis

15. Brain metastases or spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 14 days prior to study treatment start. Patients with suspected brain metastases at Screening should have a CT/MRI of the brain prior to study entry.

16. QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms. Any clinically significant abnormalities detected, require triplicate ECG results and a mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs.

17. History of active primary immunodeficiency

18. Active infection, including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen result), hepatitis C, or human immunodeficiency virus (positive HIV 1 / 2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and the absence of HBV surface antigen) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).

19. Receipt of live, attenuated vaccine within 30 days prior to the first dose of tremelimumab monotherapy. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.

20. Female patients who are pregnant or breast-feeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of tremelimumab monotherapy or MEDI4736 monotherapy and 180 days after the last dose of MEDI4736 + tremelimumab combination therapy

21. Known allergy or hypersensitivity to IP or any IP excipient

3.3 Patient enrolment and randomization

Investigators should keep a record, the subject screening log, of subjects who entered pre-study screening.

At Screening (Days -28 to -1), the Investigators or suitably trained delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign the potential patient a unique 7-digit enrollment number, beginning with "E#." This is obtained through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment

code at the center). Enrollment numbers will start at 001 in each center and go up sequentially (eg, at Center 01, patients will be assigned enrollment numbers E0101001, E0101002, etc). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

3. Obtain tumor sample and send for PD-L1 expression. Patients must be able to undergo a newly acquired tumor biopsy during screening (strongly encouraged) or to provide an available tumor sample prior to screening. The fresh or archived sample must be received by the central laboratory prior to dosing. Tumor lesions used for newly acquired biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. Samples with limited tumor content and fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component. The tumor specimen should be of sufficient quantity to allow for PD-L1 IHC and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin embedded blocks. Fresh samples, if necessary, should be obtained as the last step in the screening process, after the patient has been confirmed to meet all other inclusion criteria and confirmed not to meet any exclusion criteria.

4. Determine patient eligibility (see Sections 3.1 and 3.2)

If the patient is ineligible and not enrolled, the IVRS/IWRS should be contacted to terminate the patient in the system.

Patients will begin treatment on Day 1. Patients must not be treated unless all eligibility criteria have been met. If same-day treatment is not possible, then the study treatment should begin within 3 working days of registration.

Following confirmed PD on tremelimumab monotherapy or during follow-up, patients who meet all criteria have the option to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, at the discretion of the Investigator. See Section 3.5 and 7.2.3 for details.

If a patient withdraws from participation in the study, then his or her enrollment code or patient identification number cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized patient

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be enrolled or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is enrolled in error, and incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the

investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

This is a single-arm study in which all patients who experience confirmed PD on tremelimumab monotherapy or during follow-up will have the option to sequence to either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, if the patient meets the required criteria (see Section 7.2.3). The choice of sequencing to either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy is at the Investigator's discretion.

3.6 Methods for ensuring blinding (Not Applicable)

This is not a blinded study.

3.7 Methods for unblinding (Not Applicable)

This is not a blinded study.

3.8 Restrictions

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

1. Female patient of child bearing potential

   Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception from screening and must agree to continue using such precautions 90 days after the last dose of tremelimumab monotherapy or MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy; cessation of birth control after this point should be discussed with a responsible physician. Female patients must use a hormonal method in addition to a barrier method (ie, male condom plus spermicide) to ensure pregnancy does not occur. Not engaging in sexual activity is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should refrain from breastfeeding and egg cell donation throughout this period.

   It is strongly recommended for the male partner of a female patient to also use a male condom plus spermicide throughout this period.

   – Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as 12 months with no menstruation without an alternative medical cause).

– Effective methods (including highly effective methods) of contraception are described in Table 1. A highly effective method of contraception is defined as 1 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.

2. Male patients with a female partner of childbearing potential.

Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from Day 1 and for 90 days after the last dose of tremelimumab monotherapy or MEDI4736 monotherapy or 180 days after the final dose of MEDI4736 + tremelimumab combination therapy. 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 same period.

It is strongly recommended for the female partner of a male patient to also use an effective method of contraception throughout this period (Table 1).

All patients: Patients should not donate blood while participating in this study and for 3 months following the last dose of study treatment.

Table 1 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 patients must use an effective method of birth control.
[b] Not highly effective (ie, failure rate of ≥1% per year)
[c] A combination of male condom with either female cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered acceptable, but not highly effective, birth control methods.
[d] This is also considered a hormonal method.
[e] Highly effective (ie, failure rate of <1% per year)

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP (tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy) if any of the following occur:

- Withdrawal of consent from further treatment with IP. (The patient is at any time free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment may choose to continue to participate in the study [ie, a patient may discontinue treatment but not discontinue the study, such that the patient no longer receives treatment with IP but still participates in other study-related procedures, as necessary].)
- An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing
- Any AE that meets criteria for discontinuation
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or Sponsor, warrants withdrawal from study treatment (eg, refusal to adhere to scheduled visits)
- Lost to follow-up
- Initiation of alternative anticancer therapy including another investigational agent other than the specified subsequent study treatments included in this study
- Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with IP

Patients who develop brain metastases while on study may continue on tremelimumab monotherapy, be sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, and continue on MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy provided that the patients are asymptomatic from the brain metastases, have not required the use of steroids (>10 mg of prednisone equivalents) or anticonvulsants within 14 days of retreatment, and have shown no progression in the brain for at least 28 days after treatment.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, subjects are free to discontinue investigational product without prejudice to further treatment. A subject that decides to discontinue the IP will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Section 6.3.2). All study drugs should be returned by the subject. The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment. Prior to discontinuing a patient from study therapy, it is strongly recommended that the patient's case be discussed with AstraZeneca in consultation with the treating physician.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter long-term follow-up (see Table 3). All patients will be followed for survival until the end of the study. Subjects who decline to return to the site for evaluations should be contacted by telephone every 2 months as an alternative unless consent is withdrawn.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled. These patients should have the reason for study withdrawal recorded as 'eligibility criteria not fulfilled' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not enrolled patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn subjects will not be replaced.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 9.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse continuing participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor, trial (study) patients are placed at undue risk because of clinically significant findings that:

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

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRFs. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests. If this study is discontinued, all other studies involving tremelimumab or MEDI4736 will remain open to enrollment and screening, if deemed appropriate by the Sponsor.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2 presents the procedures for the screening and 12-month treatment and retreatment periods for all treatment groups in this study (tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy). The procedures for the follow-up period are presented in Table 3.

Table 2 Schedule of study procedures for the tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy and retreatment periods (12 months)

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see Section
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days													
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Informed consent															
Informed consent: study procedures	X[a]														3.3
Study procedures															
Physical examination (full)[b]	X														5.2.2
Targeted physical exam (based on symptoms)[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.2
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.4
ECG[d]	X	As clinically indicated													5.2.3
Concomitant medications	X	X	All visits												7.7
Palliative radiotherapy[e]	As clinically indicated														7.7
Demography	X														4.1
Previous treatments for tumor type	X														4.1
Medical/surgical history	X														4.1
Tobacco and alcohol use	X														4.1
Eligibility criteria	X														3.1, 3.2
Laboratory assessments															
Clinical chemistry (complete clinical chemistry panel including liver enzymes)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Hematology[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1

Table 2 Schedule of study procedures for the tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy and retreatment periods (12 months)

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see Section
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days													
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Urinalysis[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Hepatitis B and C and HIV	X														5.2.1
Urine hCG or serum β-hCG[h]	X	X[f]	As clinically indicated												5.2.1
Coagulation parameters[f]	X	As clinically indicated													5.2.1
Monitoring															
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.3.2
AE/SAE assessment	X	X	All visits												6.3
Pharmacokinetics															
Tremelimumab monotherapy PK sample (serum)[i]		X[i]	X[j]		X[i]			X[i]							5.4
MEDI4736 monotherapy PK sample (serum)[i]		X[i]	X[j]		X[i]			X[i]							5.4
Tremelimumab combination therapy PK sample (serum)[i]		X[i]	X[j]		X[i]			X[i]							5.4
MEDI4736 combination therapy PK sample (serum)[i]		X[i]	X[j]		X[i]			X[i]							5.4
IP administration															
Tremelimumab monotherapy															
Tremelimumab[k]		X	X	X	X	X	X	X			X			X	7.2.1
MEDI4736 monotherapy (sequenced treatment)															
MEDI4736[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	7.2.1
MEDI4736 + tremelimumab combination therapy (sequenced treatment)															

Table 2 Schedule of study procedures for the tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy and retreatment periods (12 months)

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see Section
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days													
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Tremelimumab[k]		X	X	X	X										7.2.1
MEDI4736[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	7.2.1
Other laboratory assessments and assays															
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation) for tremelimumab in tremelimumab-based treatment groups only[l]		X	X		X			X							5.4
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation) for MEDI4736 in MEDI4736-based treatment groups only[l]		X	X		X			X							5.4
Circulating soluble factors[l]		X	X		X										5.5
Tumor biopsy (freshly obtained or archival)[m]	X														5.5
Whole blood for gene expression (PaxGene-RNA tubes)[l]		X	X												5.5
Myeloid-derived suppressor cells (Cyto-Chex tube)[l]		X													5.5
PBMCs[l]		X	X												5.5
Tumor assessment (CT or MRI) (RECIST 1.1)[n]	X	UBC and TNBC: q8w relative to the date of first infusion of IP, until confirmed progression PDAC: q6w for the first 48 weeks relative to the date of first infusion of IP, and then q12w thereafter until confirmed progression													5.1

[a] Informed consent includes consent for study procedures and biopsy for PD-L1 status. For patients undergoing retreatment or sequencing to MEDI4736 or MEDI4736 + tremelimumab, an additional biopsy is not required.

[b] Body weight recorded at all physical examinations. Height is only measured at Screening.

[c] Blood pressure and pulse will be evaluated prior to the beginning of the infusion, at 30 minutes (±5 minutes) during treatment, at the end of infusion (60 minutes ±5 minutes), and in the 1-hour post-infusion observation period (60 minutes [±5 minutes] after the infusion) (ie, 120 minutes [±5 minutes] from the start of the infusion) for the first infusion only and then for subsequent infusions as clinically indicated. These assessments should be followed for each of the component infusions. Body temperature and respiratory rate will be evaluated pre-dose (prior to each infusion).

[d] ECG will be performed at Screening and as clinically indicated. For clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation.

[e] Local palliative radiotherapy for pain management is acceptable; however, if a target lesion is irradiated, that information must be captured.

[f] If screening laboratory assessments are performed within 3 days prior to Day 1, then tests do not need to be repeated at Day 1. Hematology, serum chemistry, and liver enzymes results must be available and reviewed before each dose of therapy. At any time per the Investigator's clinical judgment, more frequent serum chemistry or LFT monitoring is allowed as clinically indicated. Coagulation tests include activated partial thromboplastin time, prothrombin time, and international normalized ratio. Gamma glutamyltransferase tested at Screening, Day 1, and as clinically indicated.

[g] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[h] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[i] On Week 0 (Day 1), Week 12, and Week 24, PK samples will be collected pre-dose (within 6 hours prior to treatment with any IP, i.e prior to the 1st investigational product's infusion on the scheduled day), within 10 minutes after tremelimumab infusion completion (for tremelimumab monotherapy or MEDI4736 + tremelimumab combination therapy only), and at the end of MEDI4736 infusion (for MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy only). PK samples will be collected similarly for patients receiving tremelimumab monotherapy and for patients who receive subsequent study treatment with MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. A follow up PK sample collection for tremelimumab is required for MEDI4736+tremelimumab combination therapy at week 24.

[j] At Week 4, PK samples will be collected pre-dose (within 6 hours prior to treatment with any IP) only. PK samples will be collected similarly for patients receiving tremelimumab monotherapy and for patients who receive subsequent study treatment with MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy.

[k] All patients will be enrolled into tremelimumab monotherapy, study treatment should begin within 3 days of registration. After confirmed disease progression with tremelimumab monotherapy or during follow-up, patients may be sequenced to treatment with MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy for up to 12 months or until disease progression, whichever comes sooner (see Section 7.2.3 for details). In cases of unequivocal PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient before sequencing. For the combination therapy only - tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be conducted at the Investigator's discretion (suggested 30 minutes after each MEDI4736 and tremelimumab infusion).

[l] Samples collected pre-infusion at the scheduled visits.

[m] The fresh or archived sample must be received by the central laboratory prior to dosing. Fresh samples, if necessary, should be obtained as the last step in the screening process, after the patient has been confirmed to meet all other inclusion criteria and confirmed not to meet any exclusion criteria. The collection of tumor biopsies at the time of confirmed PD on tremelimumab or during follow-up prior to dosing with MEDI4736-based regimen and at discontinuation of study treatment is strongly encouraged, when clinically feasible.

[n] RECIST 1.1 assessments will be performed on CT (preferred) or MRI scans, either preferred with IV contrast, of the chest, the abdomen (including liver and adrenal glands), and the pelvis, as necessary based on tumor type. Additional anatomy may be imaged based on signs and symptoms of individual patients. Baseline assessments, ideally, should be performed as close as possible to the start of study treatment. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of the first infusion of IP) and no less than 4 weeks after the initial assessment of CR/PR and PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of the first infusion of IP). All confirmatory scans should be recorded on the database.

Note: For "retreatment" patients who go on to have a subsequent 12 months of treatment, the same assessments should be done as in the first 12-month treatment period with the exception of the PK, ADA, and MDSCs assessments, which do not need to be collected a second time.

Note: Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.

Note: All assessments to be performed pre-infusion unless stated otherwise.

Abbr: ADA Anti-drug antibody; AE Adverse event; β-hCG beta-Human chorionic gonadotropin; C Cycle; CR Complete response; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; HIV Human immunodeficiency virus; IP Investigational product; LFT Liver function test; MDSC Myeloid-derived suppressor cell; MRI Magnetic resonance imaging; PBMC Peripheral blood mononuclear cell; PD Progressive disease; PDAC Pancreatic ductal adenocarcinoma; PD-L1 Programmed cell death ligand 1; PK Pharmacokinetics; PR Partial response; q6w Every 6 weeks; q8w Every 8 weeks; q12w Every 12 weeks; RECIST 1.1 Response Evaluation Criteria In Solid Tumors; RNA Ribonucleic acid; SAE Serious adverse event; TNBC Triple-negative breast cancer; TSH Thyroid-stimulating hormone; UBC Urothelial bladder cancer.

Table 3 Schedule of follow-up study procedures (upon completion of therapy)

Evaluation	Time since End of Treatment[a]/Discontinuation[b]								
	Day (±3)	Months (±1 week)						12 months and every 6 months thereafter (±2 weeks)	For details see Section
	30	2	3	4	6	8	10		
Physical examination (full)[c]	X								5.2.2
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X								5.2.4
Urine hCG or serum β-hCG[d]	X								5.2.1
AE/SAE assessment	X	X	X						6.3
Concomitant medications	X	X	X						7.7
Palliative radiotherapy	As clinically indicated →								NA
ECOG performance status	At time points consistent with tumor assessments up to confirmed disease progression. Upon confirmation of progression, ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.								5.3.2
Subsequent anticancer therapy[e,f]	X	X	X	X	X	X	X	X[f]	NA
Survival status (for patients who refuse to return for evaluations and agree to be contacted, phone contact will be used)		X		X	X	X	X	X (every 2 months)	5.1
Hematology	X	X	X						5.2.1
Clinical chemistry	X	X	X						5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[g]	X								5.2.1
Tremelimumab monotherapy PK assessment[i]			X						5.4
MEDI4736 monotherapy PK assessment[i]			X						5.4
Tremelimumab combination therapy PK assessment[i]			X[h]						5.4
MEDI4736 combination therapy PK assessment[i]			X[h]						5.4

Table 3 Schedule of follow-up study procedures (upon completion of therapy)

Evaluation	Time since End of Treatment[a]/Discontinuation[b]								
	Day (±3)	Months (±1 week)						12 months and every 6 months thereafter (±2 weeks)	For details see Section
	30	2	3	4	6	8	10		
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation) for tremelimumab in tremelimumab-based treatment groups only[i]			X		X[j]				5.4
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation) for MEDI4736 in MEDI4736-based treatment groups only[i]			X		X[j]				5.4
Circulating soluble factors (to assess cytokines, chemokines, growth factors, and antibodies against tumor and self antigens in circulation)[j]	X								5.5
Whole blood for gene expression (PaxGene-RNA tubes)[j]	X								5.5
PBMCs[j]	X								5.5
Tumor assessment (CT or MRI)	For patients who **achieve disease control following 12 months of treatment**, tumor assessments should be performed as follows: q8w ±1 week (for patients with UBC or TNBC) or q12w ±1 week (for patients with PDAC) relative to the date of **first infusion** of IP until confirmed PD by RECIST 1.1 by investigational site review. For patients in the MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy groups, tumor assessments will be performed according to Table 2 relative to the first infusion subsequent study treatment. Please refer to Table 2 for timings of confirmatory scans. For patients who **discontinue tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy due to toxicity or a reason other than confirmed PD, including symptomatic deterioration**, tumor assessments should be performed relative to the date of **first infusion** of IP as follows: • UBC and TNBC: q8w ±1 week (per Table 2) until confirmed PD by RECIST 1.1 by investigational site review. • PDAC: q6w ±1 week for the first 48 weeks (per Table 2, then q12w ±1 week until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 2 for timings of confirmatory scans.								5.1

[a] It applies for tremelimumab monotherapy, MEDI monotherapy and MEDI4736 + tremelimumab combination therapy.

[b] When the decision is made that study treatment will be discontinued, please refer to section 3.9, except the patient is non-compliant with sthe study protocol or lost to follow-up.

[c] Includes weight.

[d] Pre-menopausal female patients of childbearing potential only.

[e] Patients who have PD or discontinue from treatment should be followed every 6 months for subsequent therapy.

[f] For patients who have completed 12 months of treatment and achieved disease control only, calls should be made every 2 months.

[g] fT3 and fT4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[h] For patients receiving MEDI4736 + tremelimumab combination therapy, they will have a PK assessment for each individual component (ie, 1 PK assessment for MEDI4736 and 1 PK assessment for tremelimumab.

[i] For tremelimumab, the sample collection time points start from last dose time of tremelimumab in combination therapy. The PK and ADA assessments, do not need to be collected during retreatment follow-up period.

[j] Only for those patients who have completed 12 months of treatment (not applicable for retreatment patients) and achieved disease control.

Abbr: ADA Anti-drug antibody; AE Adverse event; β-hCG beta-Human chorionic gonadotropin; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; MRI Magnetic resonance imaging; NA Not applicable; PBMC Peripheral blood mononuclear cell; PD Progressive disease; PDAC Pancreatic ductal adenocarcinoma; PK Pharmacokinetic; q6w Every 6 weeks; q8w Every 8 weeks; q12w Every 12 weeks; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1; SAE Serious adverse event; TNBC Triple-negative breast cancer; TSH Thyroid-stimulating hormone; UBC Urothelial bladder cancer.

4.1 Enrolment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in Table 2. Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained as well as information on previous treatments for the tumor type.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply a sample of their tumor (archival or fresh biopsy) for entry into this study. This consent is included in the main patient informed consent form (ICF).

All screening procedures must be performed within 28 days before the first dose of tremelimumab monotherapy (Days -28 to -1), unless otherwise specified. Screening evaluations may be performed over more than 1 visit. The fresh or archived tumor sample must be received by the central laboratory prior to dosing. Fresh samples, if necessary, should be obtained as the last step in the screening process, after the patient has been confirmed to meet all other inclusion criteria and confirmed not to meet any exclusion criteria.

4.2 Treatment period

All procedures to be conducted during the 12-month treatment period will be performed according to the assessment schedule (see Table 2). A cycle of treatment is scheduled to last 4 weeks (28 days).

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

4.3 Follow-up period

All procedures to be conducted during the 12-month follow-up period will be performed according to the assessment schedule (see Table 3). Patients who have confirmed PD while on tremelimumab monotherapy or during follow-up and subsequently receive MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy will follow Table 2 while on therapy.

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

RECIST 1.1 criteria will be used to assess patient response to treatment by determining ORR, DoR, DCR, and PFS. The RECIST 1.1 guidelines for measurable, non-measurable, target, and nontarget lesions and the objective tumor response criteria (CR, PR, SD, or PD) are presented in Appendix D. OS will also be evaluated.

The methods of imaging tumor burden used at baseline are CT (preferred) or MRI scans, preferably with IV contrast, of the chest, the abdomen (including liver and adrenal glands), and the pelvis, as necessary based on tumor type. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. All on-study assessments should utilize the same mode of scanning (CT or MRI) as baseline scans for accurate comparisons.

The baseline assessment should be performed no more than 28 days before the start of tremelimumab monotherapy and, ideally, as close as possible to the start of treatment. For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy following confirmed PD on tremelimumab monotherapy or during follow-up, a new baseline assessment should be performed no more than 28 days before the start of either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy and, ideally, as close as possible to the start of the sequenced treatment. If the scan confirming PD on tremelimumab monotherapy occurs within 28 days of the first dose of sequencing therapy, this scan may be used as the baseline scan for sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. See Section 7.2.3 for details on sequencing criteria. Efficacy for all patients will be assessed by objective tumor assessments as follows according to their tumor type. Additional tumor types may be added at the discretion of the Sponsor.

UBC and TNBC: Every 8 weeks (q8w; ±1 week) relative to the date of first infusion of IP (see Table 2 and Table 3) until confirmed progression

PDAC: Every 6 weeks (q6w; ±1 week) for the first 48 weeks relative to the date of first infusion of IP (see Table 2 and Table 3) and then q12w (±1 week) thereafter until confirmed progression

Confirmed objective disease progression is defined by RECIST 1.1 (irrespective of the reason for stopping treatment/or subsequent therapy). If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of first infusion of IP).

For patients who discontinue treatment due to toxicity in the absence of confirmed objective progression, objective tumor assessments should be continued as described above until confirmed objective disease progression.

In addition to the required confirmatory scan for PR and CR, a confirmatory scan is also required following the initial demonstration of PD. In cases of unequivocal PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with tremelimumab monotherapy may continue between the initial assessment of progression and confirmation for progression. Progression would be considered confirmed per RECIST 1.1 criteria available in Appendix D. Sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after confirmation of progression on tremelimumab monotherapy or during follow-up is at the Investigator's discretion. Treatment with sequenced therapy will begin not less than 42 days and not more than 120 days after the last dose of tremelimumab monotherapy. For patients who have confirmed PD during the tremelimumab monotherapy follow-up period, treatment with sequenced therapy will not be more than 60 days after confirmed progression.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

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

Objective tumor response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

Following confirmed disease progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the study plan (Table 3). An exception is patients with confirmed PD who continue to receive IP at the discretion of the Investigator (after consultation with AstraZeneca) or who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. Patients who continue on therapy after confirmed PD can receive treatment for a maximum of 12 months. In addition, patients who have PD or discontinue from treatment should be followed every 6 months for subsequent therapy.

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month tremelimumab monotherapy treatment period, or the 12-month MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy treatment period (after sequencing), will enter follow-up. Any of these patients who then develop PD (with or without confirmation according to RECIST 1.1) during the follow-up period may restart their treatment for another 12 months with the same treatment guidelines followed previously. In addition, patients receiving combination therapy who complete the 4 dosing cycles with MEDI4736 + tremelimumab (with clinical benefit per Investigator's judgment), but subsequently experience progression (according to RECIST 1.1) during treatment with MEDI4736 alone, will be given the option to restart MEDI4736 + tremelimumab combination therapy. See Section 7.2.2 for eligibility criteria for restarting treatment. Tumor assessment scans should occur as described above and in Table 2 (relative to the date of first infusion of IP, ±1 week) until confirmed disease progression.

It is important to follow the assessment schedule as closely as possible. Refer to the study plans (Table 2 [screening and the treatment period], Table 3 [for follow-up period]), and Appendix D.

5.1.1 Central reading of scans

Blinded Independent Central Review (BICR) assessments are not planned for this study. However, all images will be collected centrally so that the scans will be available if such verification becomes necessary. The decision to perform a BICR is at the discretion of the Sponsor. If performed, BICR will include RECIST 1.1, RECIST 1.1 modified for confirmation of progression, and irRECIST 1.1. Guidelines for imaging collection and storage will be provided in a separate document. The management of patients will be based solely upon the results of assessment conducted by the Investigator.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, thyroid function and urinalysis will be taken at the times indicated in Table 2 and Table 3.

Clinical laboratory safety tests, including serum or urine pregnancy tests for women of childbearing potential, will be performed in a qualified local clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date and results will be recorded on the appropriate eCRF.

The following laboratory variables to be measured are presented in Table 4 (clinical chemistry), Table 5 (hematology), and Table 6 (urinalysis).

Table 4 Clinical chemistry

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
ALT	Lipase
Amylase	Magnesium
AST	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid

[a] If total bilirubin is ≥2×ULN (and evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.
[b] At Screening, Day 1, and as clinically indicated.
Abbr: ALT Alanine aminotransferase; AST Aspartate aminotransferase; ULN Upper limit of normal.

Table 5 Hematology

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

Table 6 Urinalysis

Bilirubin	Leukocytes
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity
Ketones	

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells.

Table 7 Other laboratory safety assessments

Coagulation	**Thyroid function tests**
PT	fT_3[a]
APTT	fT_4[a]
INR	TSH[a]
Serology	
HIV antibodies	
Hepatitis B surface antigen;	
Anti HCV IgG	

[a] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at screening and as clinically indicated.

Abbr: APTT Activated partial thromboplastin time; fT_3 Free triiodothyronine; fT_4 Free thyroxine; HCV Hepatitis C virus; HIV Human immunodeficiency virus; IgG Immunoglobulin G; INR International normalized ratio; PT Prothrombin time; TSH Thyroid-stimulating hormone.

If a patient shows an AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN, refer to Appendix C for further instructions. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. All patients with an elevated AST, ALT, or bilirubin value (the latter at ≥1.5×ULN) at the time of the last dose of study treatment should have a further liver chemistry profile (AST, ALT, bilirubin, and alkaline phosphatase) performed 30 days (±3 days) after permanent discontinuation of study treatment.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 6.3.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to Grade 1 or 2, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later.

5.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (see Table 2 and Table 3). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems. All physical examinations include body weight measurement. Height will be measured only at Screening. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 6.3.7.

5.2.3 ECG

Resting 12-lead ECGs will be recorded according to the assessment schedule (see Table 2). ECGs should be obtained after the patient has been in a supine position for 5 minutes and should be recorded while the patient remains in that position.

ECG will be recorded at Screening and as clinically indicated.

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

ECG measurements will include heart rate, PR interval, QT interval, RR interval, and QRS complex.

Situations in which ECG results should be reported as AEs are described in Section 6.3.7.

5.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules (see Table 2 and Table 3).

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

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

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes, that is, the beginning of the infusion)
- At 30 minutes during the infusion (halfway through infusion) (±5 minutes)
- At the end of the infusion (approximately 60 minutes ±5 minutes)
- A 1-hour post-infusion observation period (60 minutes [±5 minutes] after the infusion, ie, 120 minutes [±5 minutes] from the start of the infusion) is required after the first infusion of tremelimumab or MEDI4736. For the combination therapy group, these assessments should be followed for each of the 2 component infusions. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested approximately 30 minutes after the infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional

monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.7.

Body temperature will be measured in degrees Celsius at the visits indicated in Table 2 and Table 3. The assessment will be prior to each infusion on the dosing days.

5.2.5 Other safety assessments

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum beta-hCG) samples will be performed for pre-menopausal women of childbearing potential at the times specified in the assessment schedule (see Table 2 and Table 3). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible and must be discontinued from treatment. In the event of a suspected pregnancy during the study, the test should be repeated.

Other safety tests to be performed at Screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, HIV antibodies, thyroid stimulating hormone, free triiodothyronine, and free thyroxine.

5.3 Other assessments

5.3.1 Patient reported outcomes (Not Applicable)

Not applicable to this study.

5.3.2 ECOG performance status

ECOG performance status will be assessed at the times specified in the assessment schedules (see Table 2 and Table 3) based on the following:

0 = Fully active; able to carry on all pre-disease performance without restrictions

1 = Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work

2 = Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 = Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry on any self-care. Totally confined to bed or chair

5 = Dead

Any significant changes from baseline or screening must be reported as an AE.

5.4 Pharmacokinetics and immunogenicity

5.4.1 Collection of samples and determination of drug concentration

Blood samples for determination of tremelimumab and MEDI4736 concentration in serum will be obtained according to the assessment schedules (see Table 2 and Table 3).

Samples for determination of tremelimumab and MEDI4736 concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.4.2 Collection of samples to measure for the presence of anti-drug antibodies (ADA)

Blood samples will be collected to evaluate ADA responses to MEDI4736 and ADA responses to tremelimumab (see Table 2 and Table 3 for the schedule of tests).

Evaluations will be performed using a validated immunoassay. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and the positive-negative cut points will be statistically determined from drug-naïve validation samples. Samples may be utilized for further characterization of the ADA response, including possible assessment of neutralizing antibody.

5.4.3 Storage and destruction of pharmacokinetic/anti-drug antibodies samples

PK and ADA samples, if not exhausted by analyses outlined herein, may be retained for 15 years from the last patient last visit date for research purposes.

PK and ADA samples may be disposed of or destroyed or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the Clinical Study Report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Validation Report.

Any residual material collected for PK-based analyses may be used for future exploratory biomarker research (in this case, samples will be shipped to the Biobank as designated by AstraZenenca; see details in the Laboratory Manual).

5.5 Biomarker analysis

The patient’s consent to the use of donated biological samples is mandatory.

Pretreatment tumor PD-L1 expression will be evaluated in all patients. Whenever tissue biopsy is feasible, tumor PD-L1 expression will also be assessed following progression on tremelimumab or on MEDI4736-based regimens. Putative associations with clinical endpoints will be assessed. Tumor requirements are briefly described in Section 5.5.1.

Based on availability of tissue, additional exploratory biomarkers may be evaluated as described in Section 5.5.1.1. Also, descriptions of exploratory, peripheral measures are described in this section. Samples will be obtained according to the assessment schedules provided in Table 2 and Table 3. Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Exploratory measures using the plasma samples obtained at pretreatment and following tremelimumab monotherapy may be completed in an effort to understand immunomodulatory effects.

Biomarker results may be pooled with biomarker data from other tremelimumab and MEDI4736 studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at facilities designated by AstraZeneca and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy.

5.5.1 Evaluation of candidate, predictive markers - Tumor PD-L1

Provision of tissue for PD-L1 IHC is as follows:

- MANDATORY: Provision of a tumor biopsy formalin fixed and embedded in paraffin. A freshly collected tumor biopsy is preferred; however, an archival sample is acceptable. This sample must be received by the central laboratory prior to dosing. Fresh samples, if necessary, should be obtained as the last step in the screening process, after the patient has been confirmed to meet all other inclusion criteria and confirmed not to meet any exclusion criteria.

  Samples should be collected via a core needle (18 gauge or larger) or be collected as an excisional or incisional tumor biopsy sample.

  When tissue is newly obtained for the purpose of entry into the study, 2 cores should be placed in formalin and processed to a single paraffin embedded block, as described in the Laboratory Manual.

  The tumor specimen submitted (as described in the inclusion criteria in Section 3.1) should be of sufficient quantity to allow for PD-L1 IHC analyses (see the Laboratory Manual). Newly acquired or archival specimens with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component.

Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy. If a RECIST 1.1 target lesion is used for biopsy, the lesion must be ≥2 cm in the longest diameter and must be biopsied outside of the screening period.

- The collection of tumor biopsies at the time of confirmed PD on tremelimumab or during follow-up prior to dosing with the MEDI4736-based regimens is strongly encouraged. Data obtained from such specimens will aid in establishing tremelimumab-induced biological changes in the tumor microenvironment. The biopsy procedure should be omitted if there is unacceptable clinical risk or if the procedure is otherwise considered not feasible. The Investigator must consult with the Study Physician if such sampling is not feasible. All specimens may be assessed for PD-L1 as well as the exploratory markers described below.

- The collection of tumor biopsies at study treatment discontinuation, including at disease progression on MEDI4736-based regimens. The collection of additional biopsies upon discontinuation of study treatment is strongly encouraged to enable discovery efforts (ie, identification of factors rendering tumors nonresponsive to immunotherapy).

An additional biopsy is not required for patients restarting tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy following completion of 12 months of treatment.

Additional tumor biopsies collected as part of clinical care (eg, for mixed responses or upon PD) may be submitted for exploratory analyses. Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. Please consult the Laboratory Manual for specific instructions and guidelines regarding sections.

Please review the Laboratory Manual for further details of requirements including sample quality control and shipping.

A brief description of exploratory tumor markers likely to be explored by IHC or ribonucleic acid (RNA) analysis is provided in Section 5.5.1.1.

The Ventana PD-L1 IHC assay will be used to determine PD-L1 IHC status in this study. The Ventana PD-L1 IHC analysis will be performed at a Ventana approved College of American Pathologists/Clinical Laboratory Improvement Act laboratory.

To meet the requirement of Food and Drug Administration (FDA) approval of a companion diagnostic, sections of the tumor will be retained at Ventana for potential additional studies, as requested by the FDA, to support the test approval.

5.5.1.1 Exploratory biomarkers - tumor and blood-based

Blood and tumor samples for exploratory biomarker analyses will be obtained according to the schedule presented in Table 2 and Table 3. Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Pharmacodynamic changes in biomarker measures will be monitored, when applicable. Baseline measures and early, on-treatment changes will be correlated with outcomes to identify candidate prognostic/predictive markers. Data will be reviewed in aggregate and in individual indications.

The exploratory biomarker plan is described by sample type below.

Tumor markers (in formalin-fixed, paraffin-embedded tissue)

Tissue obtained as part of screening procedures (or at progression) and for establishing PD-L1 status will be analyzed for additional markers by IHC. At a minimum, a goal is to complete CD8 and CD4/FoxP3 measures in an effort to enumerate cytotoxic versus regulatory T cells. Based on availability of tissue, a panel of additional, immune-relevant markers expressed on TILs or on tumor cells may be assessed. Markers of special interest include, but are not limited to, OX40, GITR, PD-L2, Tim-3, CD137, and Lag-3.

Tissues obtained may also be assessed also for somatic mutations and/or for an interferon-gamma (IFN-γ) gene expression signature (eg, IFN-γ, CXCL9, or CXCL10) by reverse transcription quantitative polymerase chain reaction (RT-qPCR), in situ hybridization, NanoString®, and/or similar methodologies.

Whole blood gene expression (PaxGene-RNA)

Whole blood samples will be obtained before or after treatment as outlined in Table 2 and Table 3 from all patients. Total RNA will be prepared for quantification of RNA and/or micro-RNA (miRNA) expression using RT-qPCR, microarray, sequencing, NanoString, or similar methodology.

Focus is likely to be given to the expression of immunomodulatory genes previously found to be up-regulated in response to tremelimumab and/or MEDI4736 (data not shown). Pretreatment expression of such genes may indicate active immune responses that may be augmented by checkpoint inhibitor immunotherapies; correlations with outcome data will be completed on select candidate, predictive markers with the aim of characterizing useful expression thresholds for identifying patients likely to receive benefit. Similar procedures may be completed using select peripheral blood mononuclear cell (PBMC) samples described below.

Myeloid-derived suppressor cells

Recent collective findings suggest that a baseline measure of circulating myeloid-derived suppressor cells (MDSCs) may be used as a prognostic tool in different disease settings and may specifically predict the likelihood of response to ipilimumab (anti-CTLA-4 therapy)

(Kitano et al 2014, Meyer et al 2014). Flow cytometry will be completed on all patients to quantify circulating MDSC subtypes in specimens obtained at pretreatment and in specimens obtained prior to dosing with MEDI4736-based regimens. Different MDSC count thresholds will be analyzed for their ability to predict clinical benefit from tremelimumab

Peripheral blood mononuclear cells

Whole blood samples will be collected for preparation of PBMCs and storage for potential downstream analyses. A variety of assays may be pursued, including immune cell composition/activation status analyses by flow cytometry, epigenetic analyses of DNA, MDSC assessments in banked specimens, T-cell functional assays (eg, ELISPOT), tetramer analyses to monitor antigen-specific T cells, RNA/miRNA expression, and/or the assessment of the diversity and clonality of T-cell receptor gene rearrangements using DNA.

Circulating soluble factors - plasma

Plasma will be obtained before or after treatment as outlined in Table 2 and Table 3. The concentrations of a panel of cytokines and chemokines will be assessed. Focus is likely to be given to factors involved in Th1-driven immune responses, including IFN-γ, IL-18, CXCL9, and CXCL10. High pretreatment expressions (concentrations) of such factors may indicate active immune responses that may be augmented by checkpoint inhibitor immunotherapies; correlations with outcome data will be completed on select candidate predictive markers, with an aim of characterizing useful expression thresholds for identifying patients likely to receive benefit or, alternatively, for identifying patients likely to suffer drug-related AEs.

Similarly, the concentrations of a battery of immune cell ligands or receptors may be assessed. Proteins of special interest include CTLA4, PD-1, PDL1, B7-1, B7-2, and IL6R.

Plasma may also be used for the detection/quantification of autoantibodies (against tumor-associated antigens) on ProtoArray® or a similar assay platform containing antigens preselected based on documented expression in study indications. Seroconversion following treatment will be used as an indicator of overcoming tolerance. Pretreatment seropositivity against specific antigens may provide predictive value, particularly when combined with data regarding the presence of antigen-specific T cells (Yuan et al 2011). Therefore, select, candidate autoantibody measures may be evaluated for associations with clinical benefit and for directing PBMC-based antigen-directed measures as described for PBMCs above.

5.5.2 Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but

neither the patient's name nor any other personal identifiers will appear in any publication or report.

5.5.3 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research may be reported in the CSR itself, as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies involving tremelimumab or MEDI4736 to generate hypotheses to be tested in future research.

5.5.4 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix B.

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

5.5.5 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of receipt of arrival where possible.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca Biobank system during the entire life cycle.

5.5.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action will be documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results obtained from those samples.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples.
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented.
- Ensure that the laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site.
- Ensure that the patient and AstraZeneca are informed about the sample disposal.

5.6 Pharmacogenetics (Not Applicable)

Not applicable.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition (other than progression of the malignancy under evaluation) following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea or chest pain), signs (eg, tachycardia or enlarged liver) or the abnormal results of an investigation (eg, laboratory findings or ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, or follow-up), that fulfills 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/incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix A.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs and SAEs will be collected from the time the informed consent is signed through 90 days after the last dose of the last study treatment or through initiation of subsequent anticancer therapy.

6.3.2 Follow-up of unresolved adverse events

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

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Description of the AE

The grading scales found in the revised NCI CTCAE, Version 4.03, will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE, Version 4.03, can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between the IP and each AE and answer “yes” or “no” to the question, “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes.”

A guide to the interpretation of the causality question is found in Appendix A.

6.3.5 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (ie, SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.

- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.7 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.8 Hy's Law

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

6.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

6.3.10 New cancers

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

6.3.11 Deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Physician at the next monitoring visit and should be documented in the eCRF. It 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 the Study Physician as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Drug Safety or its representative within the usual timeframes.

6.3.12 Safety Data To Be Collected following the final DCO of the study

For patients continuing to receive investigational product after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment inorder to manage AEs in accordance with the Dose Modification and Toxicity Management Guidelines (see Section 6.8.1 and Appendix E). All data post the final DCO and database

closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving investigational product (or within the 90 days following the last dose of the last study treatment) post the final DCO and database closure must be reported as detailed in Section 6.4, using the paper form process.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator or study site personnel how to proceed.

The reference documents for the definition of expectedness or listedness are the IBs for tremelimumab and MEDI4736.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

6.5 Adverse Events of Special Interest

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

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

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

AESIs observed with durvalumab ± tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis

and other events involving the eye, skin, haematological and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Section 6.8.1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

6.6 Overdose

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of IP, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.7.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital

abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.7.2 Paternal exposure

Male patients must refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of tremelimumab monotherapy or MEDI4736 monotherapy or 180 days after the final dose of MEDI4736 + tremelimumab combination therapy.

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

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner.

6.8 Management of investigational product-related toxicities

The following general guidance should be followed for management of toxicities.

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

All toxicities will be graded according to NCI CTCAE, Version 4.03.

6.8.1 Specific toxicity management and dose modification information – MEDI4736 and MEDI4736+ tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 monotherapy and MEDI4736 + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines, Please see section Appendix E. The most current version of the TMGs is also available through the following link: https://tmg.azirae.com. In addition a version of the current TMGs is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which MEDI4736 and tremelimumab should be permanently discontinued (see section 3.9 of this protocol and the Dosing Modification and Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of MEDI4736 and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the MEDI4736 + tremelimumab regimen by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

6.9 Study governance and oversight

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

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca will supply tremelimumab and MEDI4736 (Table 8).

Table 8 List of investigational products for this study

Investigational product	Dosage form and strength
Tremelimumab	20 mg/mL solution for infusion
MEDI4736	50 mg/mL solution for infusion

Abbr: IV Intravenous.

7.1.1 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine-hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dehydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 5.5. The nominal fill volume is 20 mL.

Product preparation of tremelimumab for administration with an IV bag

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

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

Doses of 750 mg (for tremelimumab monotherapy) or 75 mg (for MEDI4736 + tremelimumab combination therapy) will be administered using an IV bag containing 0.9% (weight/volume) saline, with a final tremelimumab concentration ranging from 0.1 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. A volume of 0.9% (weight/volume) saline equal to the volume of tremelimumab to be added to the IV bag must be removed from the bag prior to the addition of tremelimumab. The volume of tremelimumab (37.5 mL for 750-mg dose and 3.8 mL for 75-mg dose) is then added to the IV bag, such that final concentration is within 0.1 to 10 mg/mL (IV bag volumes of 50 to 500 mL for 75-mg dose and 100 to 1000 mL for 750-mg dose). Mix the bag by gentle inversions to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Table 9 summarizes time allowances and temperatures for tremelimumab infusion.

Table 9 Time allowances and temperatures for tremelimumab infusion

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

Abbr: IV Intravenous

In the event that either preparation time or infusion time exceeds the time limits outlined in Table 9 a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

Preparations are to be in accordance with the study-specific drug handling instructions.

7.1.2 MEDI4736

MEDI4736 will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL.

Preparation of MEDI4736 for administration with an IV bag

The dose of MEDI4736 for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the MEDI4736 vial to the start of administration should not exceed:

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

A dose of 1.5 g will be administered using an IV bag containing 0.9% (weight/volume) saline or 5% (weight/volume) dextrose, with a final MEDI4736 concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.0 mL of IV solution from the IV bag prior to addition of MEDI4736. Next, 30.0 mL of MEDI4736 (ie, 1.5 g of MEDI4736) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes of 100 to 1000 mL). Mix the bag by gentle inversions to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Table 10 below summarizes time allowances and temperatures for MEDI4736 infusion.

Table 10 Time allowances and temperatures for MEDI4736 infusion

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

Abbr: IV Intravenous.

In the event that either preparation time or infusion time exceeds the time limits outlined in Table 10, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded.

Preparations are to be in accordance with the study-specific drug handling instructions.

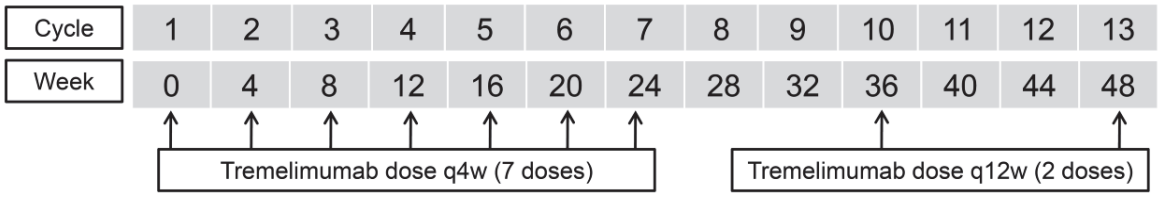
7.2 Dose and treatment regimens

7.2.1 Treatment regimens

Tremelimumab monotherapy

Patients in the tremelimumab monotherapy group will receive tremelimumab 750 mg via IV infusion q4w for 7 doses (cycles), then q12w for 2 additional doses (cycles) for up to a total of 12 months (9 doses [cycles] total) (see Figure 5).

Figure 5 Dosing scheme for tremelimumab monotherapy

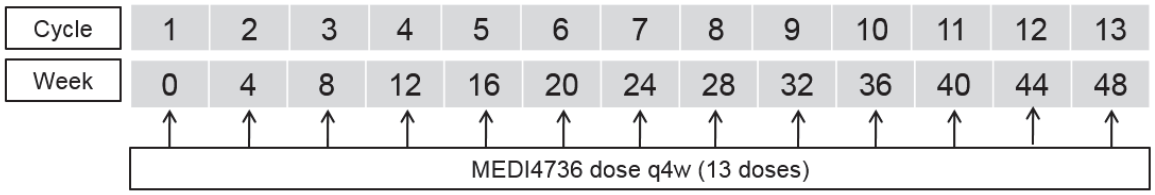


Abbr: q4w Every 4 weeks; q12w Every 12 weeks.

MEDI4736 monotherapy

Patients in the MEDI4736 monotherapy group will receive MEDI4736 1.5 g via IV infusion q4w for up to a total of 12 months (13 doses [cycles]; see Figure 6).

Figure 6 Dosing scheme for MEDI4736 monotherapy



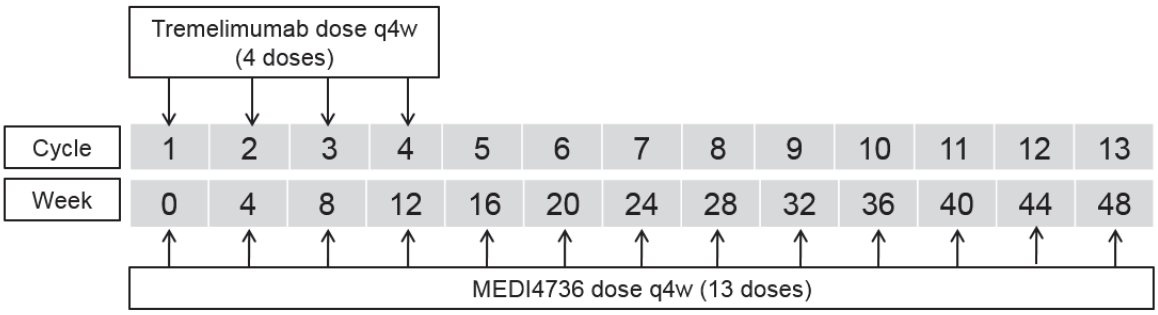
Abbr: q4w Every 4 weeks.

MEDI4736 + tremelimumab combination therapy

Patients in the MEDI4736 + tremelimumab combination therapy group will receive MEDI4736 (1.5 g via IV infusion q4w) in combination with tremelimumab (75 mg via IV infusion q4w) for up to 4 cycles each followed by MEDI4736 1.5 g via IV infusion q4w for up to a total of 8 months (9 additional doses [cycles]) (see Figure 7).

Tremelimumab will be administered first. MEDI4736 infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is recommended after the first infusion of MEDI4736 and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be conducted at the Investigator's discretion (suggested 30 minutes after each MEDI4736 and tremelimumab infusion).

Figure 7 Dosing scheme for MEDI4736 + tremelimumab combination therapy



Abbr: q4w Every 4 weeks.

7.2.2 Duration of treatment and criteria for retreatment

All treatment will be administered beginning on Day 1 for 12 months or until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met, or unless the criterion for initiating retreatment in the MEDI4736 + tremelimumab combination

therapy group is met, as described below. Patients meeting the retreatment criteria below, for their respective treatment, will follow the same treatment guidelines followed during the initial 12-month treatment period, including the same dose and frequency of treatments and the same schedule of assessments, with the exception of PK, ADA and MDSCs assessments, which do not need to be collected a second time. Also, an additional biopsy is not required for patients restarting treatment following completion of 12 months of treatment but is strongly encouraged prior to sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy (see Section 5.5.1).

Patients who meet the criteria for retreatment for their respective treatment may only receive retreatment once. Crossover from the MEDI4736 monotherapy group to the MEDI4736 + tremelimumab combination therapy group will not be permitted.

Patients receiving treatment with tremelimumab monotherapy or MEDI4736 monotherapy may undergo retreatment in 1 clinical scenario, described below:

1. Patients who achieve or maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart their assigned treatment (tremelimumab monotherapy or MEDI4736 monotherapy) upon evidence of PD, with or without confirmation and according to RECIST 1.1, during follow-up.

Patients receiving treatment with MEDI4736 + tremelimumab combination therapy may undergo retreatment in 2 clinical scenarios, described below:

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

3. Patients who complete the 4 dosing cycles of the combination of MEDI4736 and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the MEDI4736 monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may start retreatment with the combination.

For all treatment groups, before a patient starts retreatment his or her assigned treatment, the Investigator should ensure that the patient:

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

2. Still meets all of the inclusion and none of the exclusion criteria for this study

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

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

During the retreatment period, patients in the tremelimumab monotherapy treatment group will resume tremelimumab dosing at 750 mg via IV infusion q4w for 7 doses (cycles), then q12w for another 2 doses (cycles).

Patients in the MEDI4736 monotherapy treatment group will resume MEDI4736 dosing at 1.5 g via IV infusion q4w for up to a total of 12 months (up to 13 doses [cycles]).

Patients in the MEDI4736 + tremelimumab combination therapy group will resume MEDI4736 dosing at 1.5 g via IV infusion q4w with 75 mg via IV infusion of tremelimumab q4w for 4 cycles each. Patients will then continue with MEDI4736 monotherapy at 1.5 g via IV infusion q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy, up to a total of 9 additional doses (cycles) with the final dose at Week 48.

Patients who have confirmed PD during the 12-month initial treatment period with tremelimumab monotherapy, in the 12-month retreatment period, or during follow-up will have the option to initiate therapy with MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy (see Section 7.2.3). In cases of unequivocal PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient before sequencing. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression or death (whichever occurs first).

Treatment through progression and retreatment are at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. The Investigator should ensure that patients still meet all of the inclusion criteria and none of the exclusion criteria for this study and that these patients meet the following specific criteria for treatment in the setting of PD:

- Written informed consent to continue treatment in the setting of PD. This consent document will specify that treatment beyond PD is not the standard-of-care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population.
- Absence of clinical symptoms or signs indicating clinically significant disease progression and no decline in ECOG performance status to >1
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention

A patient with confirmed progression receiving tremelimumab monotherapy or MEDI4736 monotherapy cannot continue therapy or obtain retreatment if dosing is ongoing and the progression occurs in the target lesions that have previously shown a confirmed response (CR or PR). A patient with a confirmed progression receiving MEDI4736 + tremelimumab combination therapy cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy (q4w dosing) and progression occurs in thetarget lesions that have previously shown a confirmed response (CR or PR).

7.2.3 Sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy

Patients who have confirmed disease progression (with confirmation according to RECIST 1.1) at any time during tremelimumab monotherapy treatment, and who meet the necessary criteria, may be sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, at the discretion of the Investigator, upon termination of tremelimumab monotherapy treatment. Treatment with sequenced therapy in these patients will begin not less than 42 days and not more than 120 days after the last dose of tremelimumab monotherapy and will continue for up to 12 months or until disease progression (whichever comes sooner). Patients who have confirmed PD during the tremelimumab monotherapy follow-up period, and who meet the necessary criteria, may also be sequenced, in cases of unequivocal PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient before sequencing. Treatment with sequenced therapy in these patients will begin not more than 60 days after confirmed progression and will continue for up to 12 months or until disease progression (whichever comes sooner). Patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy and meet the criteria listed in Section 7.2.2 are eligible for retreatment once, upon progression (with or without confirmation), with their assigned MEDI4736-based regimen.

Patients who experience confirmed PD on tremelimumab monotherapy or during follow-up will be eligible to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy if they meet the following criteria:

1. No initiation of an alternative anticancer therapy

2. No use of steroids (>10 mg prednisone equivalents) within 14 days of first dose of MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy

3. Continue to meet inclusion criteria and do not meet any exclusion criteria for the study with the exception of providing another tumor biopsy Has had a baseline tumor assessment within 28 days of starting their sequenced treatment; all further scans should occur with the same frequency as during the initial 12 months of treatment with tremelimumab monotherapy (relative to the date of first infusion of IP) until study treatment is stopped. If the scan confirming PD on tremelimumab monotherapy occurs within 28 days of the first dose of sequencing therapy, this scan may be used as the baseline scan for sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy.

4. No Grade 3 or 4 or higher treatment-related toxicity that occurs during the tremelimumab monotherapy treatment period, including:

   – Any Grade ≥3 colitis

   – Any Grade 4 irAE

   – Any Grade 3 irAE that does not downgrade to Grade ≤2 within 3 days after onset of the event despite maximal supportive care, including systemic corticosteroids, or downgrade to Grade ≤1 or baseline within 14 days

   – Liver transaminase elevation >8×ULN or total bilirubin >5×ULN

   – Any Grade ≥2 pneumonitis that does not resolve to Grade ≤1 within 3 days of the initiation of maximal supportive care

5. The definition excludes the following conditions:

   – Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic

   – Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, or lymph nodes)

   – Dosing may continue despite concurrent vitiligo and alopecia of any AE grade

   – irAEs are defined as AEs of immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings.

6. Patients who develop brain metastases while on study may continue on tremelimumab monotherapy, be sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, or continue on assigned MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy provided that the patients are asymptomatic from the brain metastases, have not required the use of steroids (>10 mg of prednisone equivalents) or anticonvulsants within 14 days of retreatment, and have shown no progression in the brain for at least 28 days after treatment.

7. Patients who discontinue tremelimumab monotherapy due to toxicity cannot sequence to the combination of MEDI4736 + tremelimumab after confirmed PD; if they are sequenced, these patients must receive treatment with MEDI4736 monotherapy.

Post final Data Cut off (DCO)

Efficacy scans will be collected in accordance with local clinical practice. Patients who are still in progression-free follow up following the final DCO and database closure are to undergo sampling for local laboratory assessments in such a way that continued per-protocol eligibility for retreatment or sequencing with IP can be properly determined (Figure 4). For patients receiving retreatment or sequencing with IP following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with IP in order to manage AEs in accordance with the Dosing Modification and Toxicity Management Guidelines (Section 6.8.1 and Appendix E).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with IP may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

Study drug may be supplied to sites manually outside of IXRS system. Drug accountability should be managed as described in Section 7.6.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into the local language.

Labels will be provided as either a single panel label or as multi-language booklet labels.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. IPs are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The IP label on the pack/bottle/carton specifies the appropriate storage. In addition, temperature ranges for storage are described in Sections 7.1.1 and 7.1.2. Storage is also described in the IB.

7.5 Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by site reconciliation of medication dispensed and returned.

7.6 Accountability

The IPs provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs.

Study site personnel will account for all study drugs received at the site, for all unused study drugs, and for appropriate destruction of study drugs. Certificates of delivery, destruction, and return should be signed.

7.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until 90 days after the last dose of IP. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.8 for guidance on management of IP-related toxicities.

Prohibited medication/class of drug:	**Usage:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given during the study
mAbs against CTLA-4, PD-1, or PD-L1 through 90 days post last dose during the study	Should not be given during the study
Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy for nontarget lesions), or biologic or hormonal therapy for cancer treatment.	Should not be given during the study. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers.	Should not be given during the study. (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Temporary uses of corticosteroids for concurrent illnesses [eg, food allergies or CT scan contrast hypersensitivity] are acceptable upon discussion with the Study Physician.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
Herbal and natural remedies	Should be avoided during the study

Abbr: AE Adverse event; CT Computed tomography; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; IP Investigational product; mAbs Monoclonal antibody; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1.

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

7.7.1 Other concomitant treatment

Other medication other than those described in Section 7.7 that are considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post Study Access to Study Treatment

After the final analysis, AstraZeneca will continue to supply open-label drug to patients who are eligible to receive tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy (see Section 7.2). The clinical study database will be closed and only SAEs will be reported to AstraZeneca as detailed in Section 6.3.12.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All statistical analyses will be performed by AstraZeneca or its representatives. The analyses will be descriptive and no inferential analysis will be performed based on statistical tests. All evaluations will be exploratory in nature.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to database lock, and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data.

8.2 Sample size estimate

This study will screen approximately 38 patients with each selected advanced solid tumor type globally to enroll approximately 32 evaluable patients (ie, patients eligible to be included in the Full Analysis Set [FAS]). (Additional tumor types may be added at the discretion of the Sponsor.)

The study is sized to allow the use of a minimax Simon 2-Stage design (Simon 1989) within each of the tumor types according to the following assumptions and algorithms. The minimax Simon 2-Stage design as well as DCR after 2 tumor assessments will be evaluated to reduce exposure of a large number of patients to ineffective treatment, according to the algorithm below:

- H0: p0=0.02 (p0: proportion of responders under the null hypothesis)
- H1: p1=0.14 (p1: proportion of responders under the alternate hypothesis)

Algorithm:

N=32 evaluable patients, with N_1=20 and N_2=12

- If no response is observed out of the first 20 patients, the DCR data will also be evaluated to make a final decision before discontinuing the tumor cohort. (Ongoing patients will still be eligible to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy as previously described.) If ≥10 out of the first 20 patients achieve DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients may be enrolled. A final decision to continue enrollment will be made by the Sponsor after evaluating all of the available clinical data at that time.
- If 1 or more responses are observed out of the first 20 patients, enroll 12 additional patients, for a total of 32 evaluable patients for each tumor type.
  - If ≤2 responses are observed out of the 32 patients, then no further investigation of that tumor type will be done.
  - If >2 responses are observed out of the 32 patients, the null hypothesis will be rejected, and further investigation of that tumor type is warranted.

The assessment of response after the first 20 evaluable patients in the tumor types will be based on Investigator/site tumor data RECIST 1.1 assessment. This design will ensure a type I error of no more than 5% (1-sided) and an 83% power for each of the tumor types.

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 11.

Table 11 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
ORR, DoR, DCR, BoR, PFS, OS	Evaluable[a], MEDI[b] & COMBO[c] analysis sets
Demography	FAS[d]
PK data	PK Analysis Set
Safety data	
Exposure	Safety Analysis Set[e]
AEs	Safety Analysis Set[e]
Laboratory measurements	Safety Analysis Set[e]
Vital signs	Safety Analysis Set[e]

[a] The Evaluable analysis set will be used for the efficacy analysis of patients who received tremelimumab monotherapy.
[b] The MEDI analysis set will be used for patients who sequence to MEDI4736 monotherapy.
[c] The COMBO analysis set will be used for patients who sequence to MEDI4736 + tremelimumab combination therapy.
[d] The FAS will be used to summarize all enrolled patients
[e] Separate summaries will be performed for tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy
Abbr: AE Adverse event; BoR Best objective response; DCR Disease control rate; DoR Duration of response; FAS Full Analysis Set; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetic.

8.3.1 Full Analysis Set

The statistical analysis with the full analysis set (FAS) will include all enrolled patients. This analysis set will be used to summarize demography, disease characteristics and other baseline variables.

8.3.2 Evaluable Analysis Set

A subset of the FAS will include all treated patients (ie, received at least 1 dose of tremelimumab monotherapy) who have measurable disease at baseline.

8.3.2.1 MEDI Analysis Set

This analysis set is a subset of the Full Analysis Set (FAS), and it will include all patients who are treated with tremelimumab, receive at least 1 dose of MEDI4736 monotherapy, and have a baseline tumor assessment prior to MEDI4736 monotherapy dosing.

8.3.2.2 COMBO Analysis Set

This analysis set is subset of the FAS, and it will include all patients who are treated with tremelimumab, receive at least 1 dose of MEDI4736 + tremelimumab combination therapy, and have a baseline tumor assessment prior to MEDI4736 + tremelimumab combination therapy dosing.

8.3.3 Safety analysis set

All patients who received at least 1 dose of IP (tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy) will be included in the Safety Analysis Set. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set.

8.3.4 Pharmacokinetic analysis set

All patients who receive at least 1 dose of IP per the protocol for whom have at least 1 measurable PK concentration post-dose and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

8.4.1.1 RECIST 1.1-based endpoints

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrollment. For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy following confirmed progression on tremelimumab monotherapy or during follow-up, a new baseline assessment will be recorded prior to the first dose of sequenced therapy. If the scan confirming PD on tremelimumab monotherapy occurs within 28 days of the first dose of sequenced therapy, this scan may be used as the baseline scan for sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Appendix D for the definitions of CR, PR, SD, and PD.

8.4.1.2 Primary endpoint (objective response rate)

The primary endpoint is ORR. ORR (per RECIST 1.1 as assessed by the site Investigator) is defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on all treated patients who have measurable disease at baseline per the site Investigator. Therefore, if the site Investigator finds any patient who does not have measurable disease at baseline, then the analysis of ORR using site Investigator data will exclude that patient and the denominator will be all treated patients who have measurable disease at baseline per the site Investigator.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any patient who discontinues treatment without progression, receives a subsequent therapy, and then responds will not be included as responders in the ORR.

The above derivation of ORR will be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy.

For sensitivity analysis in the tremelimumab monotherapy group only, ORR may be assessed using the RECIST 1.1 site Investigator tumor data following a modification where any objective progression requires confirmation. Therefore, data obtained up until confirmed progression, or the last evaluable assessment in the absence of a confirmed progression, may be included in the assessment of ORR. Note that the response may be after an unconfirmed progression.

8.4.1.3 Secondary endpoints

Duration of response

DoR (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint. The denominator for DoR will be defined as described for ORR (see Section 8.4.1.2).

The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

The above derivation of DoR may be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy.

Sensitivity analyses of DoR may be performed in the tremelimumab monotherapy group only based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Disease control rate

DCR at 4 or 12 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 4 or 12 months, respectively, or who have demonstrated SD for a minimum interval of 16 or 52 weeks, respectively (-7 days, ie, 105 or 357 days, respectively), following the start of study treatment. DCR will be determined programmatically based on RECIST 1.1 using site Investigator data and all data up until the first progression event.

The above derivation of DCR may be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy.

Sensitivity analyses of DCR may be performed in the tremelimumab monotherapy group only based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Progression-free survival

PFS (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of enrollment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 1 day unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

In the absence of clinically significant deterioration, the investigational site is advised to continue the patients on their respective treatments until progression has been confirmed.

The above derivation of PFS may be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. PFS (per RECIST 1.1 as assessed by the site Investigator) for these patients will be defined as the time from the date of initial treatment with sequenced therapy (ie, either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression.

Sensitivity analyses of PFS may be performed in the tremelimumab monotherapy group only based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Overall survival

OS is defined as the time from the date of enrollment until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of data cut-off for the analysis, and if patients are confirmed to be alive or if the death date is post the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries.

OS for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy is defined as the time from the date of initial treatment with sequenced therapy (ie, either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy) until death due to any cause.

Best objective response

BoR is calculated based on the overall visit responses from each RECIST 1.1 assessment, described in Appendix D. It is the best response a patient has had during their time in the study up until RECIST 1.1 progression (or confirmed progression where applicable) or the last evaluable assessment in the absence of RECIST 1.1 progression.

Categorization of BoR will be based on RECIST 1.1 (Appendix D) using the following response categories: CR, PR, SD, PD, and NE.

CR or PR must be confirmed. BoR will be determined programmatically based on RECIST 1.1 using site Investigator data using all data up until the first progression event.

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST 1.1 assessments prior to death.

For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs ≤17 weeks (ie, 16 weeks ±7 days) after enrollment, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks (ie, 16 weeks ±7 days) after the date of enrollment then BoR will be assigned to the NE category.

Progression events that have been censored due to them being >17 weeks after the last evaluable assessment will not contribute to the BoR derivation.

Sensitivity analyses of BoR may be performed in the tremelimumab monotherapy group only based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

8.4.2 Calculation or derivation of safety variables

8.4.2.1 Adverse events

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. For AEs, on treatment (or treatment emergent AEs) will be defined as any AE that started after dosing or prior to dosing and that worsens following exposure to the treatment.

Any AE occurring within 90 days of discontinuation of IP (ie, the last dose of tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy) will be included in the AE summaries.

Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of tremelimumab monotherapy, MEDI4736monotherapy, or MEDI4736 + tremelimumab combination therapy) will be flagged in the data listings. A separate data listing of AEs occurring more than 90 days after discontinuation of tremelimumab monotherapy, MEDI4736monotherapy, or MEDI4736 + tremelimumab combination therapy will be produced. These events will not be included in AE summaries.

8.4.2.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT).

QTcF = QT/RR^ (1/3) where RR is in seconds

Corrected calcium will be derived during creation of the reporting database using the following formula:

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02).

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.

- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded.

The denominator in vital signs data should include only those patients with recorded data.

8.4.3 Calculation or derivation of patient-reported outcome variables (Not Applicable)

Not applicable to this study.

8.4.4 Calculation or derivation of pharmacokinetic variables

8.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modelling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between PK exposure and the effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report.

8.4.4.2 Pharmacokinetic non-compartmental analysis

The actual sampling times will be used in the PK calculations. Tremelimumab and MEDI4736 concentration data and summary statistics will be tabulated. Individual and mean blood tremelimumab and MEDI4736 concentration time profiles will be generated. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow).

8.4.5 Calculation or derivation of immunogenicity variables

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs for tremelimumab and MEDI4736. The immunogenicity titer will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated.

8.4.6 Calculation or derivation of biomarker variables

Biomarker status will be assessed for evaluable patients according to pre-specified criteria that will be detailed in the SAP.

8.4.7 Calculation or derivation of pharmacogenetic variables (Not Applicable)

Not applicable.

8.5 Methods for statistical analyses

For each selected advanced solid tumor type, ORR will be evaluated in an ongoing basis using the Investigator's assessment of responses. Recruitment will be stopped if no response is

observed in the first 20 evaluable patients. If 1 or more response is observed among the first 20 evaluable patients, then 12 additional patients will be enrolled for a total of 32 patients.

The primary statistical analyses will be based on a minimax Simon 2-Stage design (Simon 1989) algorithm described under Section 8.2. The data cut-off for the primary analysis of all study endpoints including OS will take place approximately 12 months after the last patient completes 12 months of initial Treme monotherapy, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor. A final data cut-off of OS and safety will be conducted approximately 6 months after the primary analysis data cut-off.

Efficacy analyses will be reported separately for treatment with tremelimumab monotherapy and also for patients treated with MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. Similarly, safety analyses will be performed for the individual treatments (ie, safety analyses for tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy).

All analyses are descriptive, and no statistical testing will be performed. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total.

Baseline for tremelimumab monotherapy will be the last assessment of the variable under consideration prior to the intake of the first dose of tremelimumab therapy, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to enrollment.

For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy following confirmed PD on tremelimumab monotherapy or during follow-up, baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to sequencing.

Efficacy data will be summarized and analyzed based on the FAS, evaluable analysis set, MEDI analysis set, and COMBO analysis set (see Table 11). PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized based on the Safety Analysis Set.

Table 12 details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

Table 12 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints analyzed	Notes
Objective response rate	• N (%) and 95% exact CI using site Investigator data (RECIST 1.1) • N (%) and 95% exact CI using site Investigator data (RECIST 1.1, modified for confirmation of progression)[a]
Duration of response	Secondary analysis • Kaplan-Meier plots using site Investigator data (RECIST 1.1) • Kaplan-Meier plots using site Investigator data (RECIST 1.1 modified for confirmation of progression)[a]
Disease control rate	Secondary analysis • N (%), 95% exact CI, using site Investigator data (RECIST 1.1) • N (%), 95% exact CI using site Investigator data (RECIST 1.1 modified for confirmation of progression)[a]
Progression-free survival	Secondary analysis • Kaplan-Meier plots using site Investigator data (RECIST 1.1) • Kaplan-Meier plots using site Investigator data (RECIST 1.1 modified for confirmation of progression)[a]
Overall survival	Secondary analysis • Kaplan-Meier plots of OS
Best objective response	Secondary analysis • N (%), using site Investigator data (RECIST 1.1)[a]

[a] Tremelimumab monotherapy group only.
Abbr: CI Confidence interval; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1; OS Overall survival.

8.5.1 Analysis of the primary variable (s)

The primary analysis of each selected advanced solid tumor will follow the algorithm of testing using a minimax Simon 2-Stage design.

The primary endpoint, ORR, will be estimated with 95% exact confidence intervals (CIs). The primary analysis will be based on the programmatically derived ORR based on site Investigator assessments and using all scans, regardless of whether they were scheduled or not.

For patients who have confirmed progression on tremelimumab monotherapy or during follow- up and sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above analyses will be repeated on the primary variable (ORR).

Sensitivity analysis may be performed in the tremelimumab monotherapy group only on programmatically derived ORR using site Investigator data (RECIST 1.1 modified for confirmation of progression) to determine if there is any difference when using progression confirmation rules.

Summaries will present the number and percentage of patients with a tumor response (CR/PR). The number (%) of patients with a confirmed response and the number (%) of patients with a single visit response (ie, an unconfirmed response) will also be presented.

8.5.2 Analysis of the secondary variable(s)

Duration of response

Kaplan-Meier plots of DoR based on the site Investigator assessment of RECIST 1.1 will be presented. Median DoR will be summarized for only patients who have a response.

For patients who have confirmed progression on tremelimumab monotherapy or during follow-up and sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above analyses for DoR may be repeated.

In addition, a sensitivity analysis using DoR from the site Investigator tumor data may be done in the tremelimumab monotherapy group only (RECIST 1.1 modified for confirmation of progression) to determine the effect of confirmation of progression.

Disease control rate

The DCR based upon the site Investigator assessment of RECIST 1.1 will be summarized (ie, number of patients [%] with 95% exact CIs).

For patients who have confirmed progression on tremelimumab monotherapy or during follow-up and sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above analyses for DCR may be repeated.

In addition, a sensitivity analysis of DCR may also be summarized in the tremelimumab monotherapy group only based upon the site Investigator tumor data (for RECIST 1.1 modified for confirmation of progression).

Progression-free survival

Kaplan-Meier plots of PFS will be presented. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS.

For patients who have confirmed progression on tremelimumab monotherapy or during follow-up and sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above analyses for PFS may be repeated.

As a sensitivity analysis, summaries and Kaplan-Meier plots of PFS may be provided in the tremelimumab monotherapy group only using site Investigator data (for RECIST 1.1 modified for confirmation of progression).

Overall survival

Kaplan-Meier plots of OS will be presented per treatment group. Summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be provided along with median OS.

The proportion of patients alive at 12 months after starting treatment with tremelimumab monotherapy will be summarized (using the Kaplan-Meier curve).

For patients who have confirmed progression on tremelimumab monotherapy or during follow-up and sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above analyses for OS may be repeated.

Best objective response

BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE).

For patients who have confirmed progression on tremelimumab monotherapy or during follow-up and sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above analyses for BoR may be repeated.

In addition, a sensitivity analysis of BoR in the tremelimumab monotherapy group only may also be summarized based upon the site Investigator tumor data (for RECIST 1.1 modified for confirmation of progression).

8.5.3 Analysis of other variables (Not Applicable)

Not applicable to this study.

8.5.4 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary provided for all evaluable patients.

8.5.5 Immunogenicity

Immunogenicity results will be listed by patient, and a summary will be provided of the number and percentage of patients who develop detectable anti-tremelimumab and anti-MEDI4736 antibodies. The immunogenicity titer data will be listed for samples confirmed positive for the presence of anti-tremelimumab and anti MEDI4736 antibodies.

The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated if data allow.

8.5.6 Biomarker data

The relationship between tumor microenvironment PD-L1 expression and clinical endpoint (ORR, DoR, PFS, and OS) will be presented for a subset of patients in the FAS with measurable disease at baseline per the local Investigator and who are evaluable for each

endpoint. This will be assessed for each solid tumor type using similar summary and graphical representations to those that are outlined for the efficacy outputs.

8.5.7 Subgroup analysis (if applicable)

There are no planned subgroup analyses.

8.5.8 Interim analysis

No interim analysis for efficacy is planned for this study. However, ORR and DCR will be evaluated on an ongoing basis for the first 20 evaluable patients within a given selected solid tumor type to complete Stage 1 of the minimax Simon 2-Stage design.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures, IVRS, and WBDC.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual, and study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for the location of source data.

9.2.2 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients. In all other respects not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or before patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study." The Investigator will be notified by the Sponsor when recruitment is complete.

The study is expected to start in Q4 2015 and to end by Q2 2018.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP) or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with tremelimumab or MEDI4736.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by the AstraZeneca Data Management Centre.

Data entered in the WBDC system or data captured electronically will be immediately saved to the applicable database and changes tracked to provide an audit trail.

The data collected through third party sources will be obtained and reconciled against study data.

AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, a validated, signed and locked, clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRBs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/IRBs with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure that all patients are notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure that each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File.
- Ensure that a copy of the signed ICF is given to the patient.

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised CSP).

The amendment is to be approved by the relevant EC/IRB and, if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to EC/IRB see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC/IRB are to approve the revised ICF before the revised form is used.

If required by local regulations, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

"Life-threatening" means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of "related" is made if, following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

CREATININE CALCULATION

Cockcroft-Gault equation

$$\text{Males: } CL_{CR} = \frac{(140\text{-age}) \times (\text{kg body weight})}{(72 \times \text{mg/dL serum creatinine})}$$

$$\text{Females: } CL_{CR} = \frac{(140\text{-age}) \times (\text{kg body weight}) \times 0.85}{(72 \times \text{mg/dL serum creatinine})}$$

MEDI4736 and tremelimumab

There is no information to date on drug-drug interactions with MEDI4736 or tremelimumab either preclinically or in patients. As MEDI4736 and tremelimumab are monoclonal antibodies and therefore proteins, they will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that MEDI4736 or tremelimumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions.

No formal drug-drug interaction studies have been conducted with tremelimumab. However, in renal cell carcinoma studies, acute renal failure has been reported with the combination of tremelimumab and sunitinib.

The mechanism of action of MEDI4736 involves binding to PD-L1, and the mechanism of action of tremelimumab involves binding to CTLA-4; therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes, the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B, or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are, eg, Ebola, Lassa fever virus:

- Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, B, C, D, and E viruses, human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation, and packing should be done by an IATA-certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 5.2.1 and 6.8 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2 × ULN at any point during the study following the start of study medication, irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN

- AST ≥3 × ULN
- TBL ≥2 × ULN

The Investigator will without delay review each new laboratory report, and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section Definitions of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up
Potential Hy's Law Criteria not met
If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met
If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

The Study Physician contacts the Investigator, to provide guidance, discuss, and agree on an approach for the study patient's follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the 3 Liver eCRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and Assessment of Potential Hy's Law Cases
The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the

IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term "Hy's Law") according to AstraZeneca standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term "Potential Hy's Law"), applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required.
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section Potential Hy's Law Criteria metof this Appendix.

[#]A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law
This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection, or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at his or her first on-study treatment visit as described in Section Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Section Potential Hy's Law Criteria metof this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Section Potential Hy's Law Criteria met of this Appendix.

[#]A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix D Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D4884C00001study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least 1 measurable (by RECIST 1.1) lesion which has not been previously irradiated. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Measurable:

A lesion, not previously irradiated per the protocol prior to enrollment, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline[1]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Lesions <2 cm biopsied within the screening period (fresh tumor biopsy)

[1] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

- Previously irradiated lesions that have not demonstrated progression[2]
- Brain metastasis

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs).

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

METHODS OF ASSESSMENT
The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided in Table 13, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

[2] Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated and have not demonstrated progression will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

Table 13 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest X-ray	X-ray, Chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

Abbr: CT Computed tomography; FDG-PET 18-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

CT and MRI
CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D4884C00001 study, the methods of assessment of tumor burden used at baseline and follow-up visits are CT/MRI of the chest, abdomen (including liver and adrenal glands), and pelvis, as necessary based on tumor type. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra indicated. For brain lesion assessment, MRI is the preferred method.

Clinical examination
In the D4884C00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray
Plain X-ray
In the D4884C00001 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound
In the D4884C00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy
In the D4884C00001 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers
In the D4884C00001 study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology
In the D4884C00001 study histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Isotopic bone scan
Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D4884C00001 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

FDG-PET scan
In the D4884C00001 study, 18-Fluoro-deoxyglucose positron emission tomography (FDG PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive 18-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

TUMOR RESPONSE EVALUATION
Schedule of evaluation
RECIST assessments will be performed using CT/MRI assessments of chest, abdomen (including liver and adrenal glands), and pelvis, as necessary based on tumor type. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before start of tremelimumab monotherapy and, ideally, should be performed as close as possible to the start

[3] A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

of treatment (see Table 14 of the Clinical Study Protocol). For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy following confirmed PD on tremelimumab monotherapy, a new baseline assessment should be performed no more than 28 days before the start of either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy and, ideally, as close as possible to the start of the sequenced treatment. If the scan confirming PD on tremelimumab monotherapy occurs within 28 days of the first dose of sequencing therapy, this scan may be used as the baseline scan for sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. Follow-up assessments will be performed as follows according to tumor type until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment and/or subsequent therapy). Additional tumor types may be added at the discretion of the Sponsor.

- Urothelial bladder cancer and triple-negative breast cancer: Every 8 weeks (±1 week) relative to the date of first infusion of investigational product

- Pancreatic ductal adenocarcinoma: Every 6 weeks (±1 week) for the first 48 weeks relative to the date of first infusion of investigational product and then every 12 weeks (±1 week) thereafter

Additional assessments will be performed post confirmed objective disease progression for patients remaining on treatment, retreatment, or until subsequent cancer therapy according to the clinical study protocol.

Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Target lesions
Documentation of target lesions
A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as

the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions
This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 14).

Table 14 Evaluation of target lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

Abbr: CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 15).

Table 15 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

Abbr: CR Complete response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with "symptomatic deterioration" requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 16.

Table 16 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbr: CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no non-target lesions at baseline).

CONFIRMATION OF PROGRESSION

In the D4884C00001study, imaging for confirmation of response (complete response or partial response) should be performed at next scheduled visit (and no less than 4 weeks) following the date the criteria for response were first met.

Disease progression requires confirmation. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progression of disease (PD) in the absence of clinical deterioration.

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

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

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

- And/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first time point new lesions identified

(1)The assessment of progression requires a ≥20% increase in the sum diameters of target lesions at the first progression timepoint relative to the nadir. The nadir is the smallest sum of diameters, and this may be at baseline or subsequent follow-up assessments. The confirmatory scan confirms the persistence of the ≥20% increase relative to the nadir. The minimum absolute increase in the sum of diameters of target lesions is at least 5 mm at both assessments.

In the absence of significant clinical deterioration the Investigator should continue treatment until progression is confirmed. If progression is not confirmed, then the patient should continue on treatment and on treatment assessments.

Eligible patients who have confirmed PD on tremelimumab will have the option to be sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, at the discretion of the Investigator, provided they have not received an alternative cancer therapy and still meet continuation criteria as specified in the main original consent.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

CENTRAL REVIEW

The Contract Research Organization appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

REFERENCES

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-4

Appendix E Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion related, and Non Immune-mediated Reactions

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. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	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., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 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 of

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
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).	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.

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.

Pediatric Considerations

Dose Modifications	Toxicity Management
	– 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	**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	**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.

	consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	– 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-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 alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	**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]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. See instructions at **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** 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 or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator 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)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline.	**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.

(Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at 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.	– 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 baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-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 Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:**	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for

		Permanently discontinue study drug/study regimen.	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 drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 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 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)	**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).

		can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– For 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 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.	**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 toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	– 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).
	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:*

			○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 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 4:** Permanently discontinue study drug/study regimen.	**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:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ 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:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
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; intervention indicated)	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.

	(Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	If Grade 3-4, permanently discontinue study drug/study regimen.	– 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;	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation.

	limiting self-care ADLs)	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.	– 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.

Appendix F Change Summary

The protocol for the study is to be amended as follows:

1. Section of protocol affected:

Protocol synopsis

Previous text:
The data cut-off for the primary analysis of all study endpoints including OS, will take place approximately 12 months after the last patient completes 12 months of initial Treme Monotherapy, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor.

Revised text:
The data cut-off for the primary analysis of all study endpoints including OS, will take place approximately 12 months after the last patient completes 12 months of initial Treme Monotherapy, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor. A final data cut-off of OS and safety will be conducted approximately 6 months after the primary analysis data cut-off.

Reason for Amendment:
Make consistency with section 8.5 with final DCO of OS and safety added.

2. Section of protocol affected:

6.3.12 Safety Data To Be Collected following the final DCO of the study

Previous text:
For patients continuing to receive investigational product after final DCO and database closure, assessments will revert to the Investigator's standard of care. It is recommended that investigators monitor the patient's safety laboratory results prior to and periodically during treatment with investigational product in order to manage AEs in accordance with the toxicity management guidelines (Appendix E and Section 6.8.1). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of Serious Adverse Events, will not otherwise be reported for the purposes of this study.

All SAEs, overdoses and pregnancies that occur in patients still receiving investigational product (or within the 90 days following the last dose of the last study treatment) post the final DCO and database closure must be reported as detailed in Section 6.4, using the paper form process.

Revised text:

For patients continuing to receive investigational product after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment inorder to manage AEs in accordance with the Dose Modification and Toxicity Management Guidelines (see Section 6.8.1 and Appendix E). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving investigational product (or within the 90 days following the last dose of the last study treatment) post the final DCO and database closure must be reported as detailed in Section 6.4, using the paper form process.

Reason for Amendment:

Update to safety data collection following the final DCO of the study.

3. Section of protocol affected:

7.2.3 Sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy

Previous text:

Post final Data Cut off (DCO)

Efficacy scans will be collected in accordance with local clinical practice. Patients who are still in treatment of investigational product following the final DCO and database closure it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with investigational product in order to manage AEs in accordance with the toxicity management guidelines (please see Section 6.8.1). For patients continuing to receive investigational product after final DCO and database closure, assessments will revert to the Investigator's standard of care. It is recommended that investigators monitor the patient's safety laboratory results prior to and periodically during treatment with

investigational product in order to manage AEs in accordance with the toxicity management guidelines (Appendix E and Section 6.8.1).

Revised text:

Post final Data Cut off (DCO)

Efficacy scans will be collected in accordance with local clinical practice. Patients who are still in progression-free follow up following the final DCO and database closure are to undergo sampling for local laboratory assessments in such a way that continued per-protocol eligibility for retreatment or sequencing with IP can be properly determined (Figure 4). For patients receiving retreatment or sequencing with IP following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with IP in order to manage AEs in accordance with the Dosing Modification and Toxicity Management Guidelines (Section 6.8.1 and Appendix E).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with IP may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

Reason for Amendment:

To clarify patient management post DCO.

4. Section of protocol affected:

7.8 Post Study Access to Study Treatment

Previous text:
After the final analysis, AstraZeneca will continue to supply open-label drug to patients who are eligible to receive tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy (initial or repeat) (see Section 7.2). The clinical study database will be closed and only SAEs will be reported to AstraZeneca as detailed in Section 6.3.12. Assessments will revert to the Investigator's standard of care. I t is recommended that Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with investigational product in order to manage AEs in accordance with the toxicity management guidelines (Appendix E and Section 6.8.1). Study drug will be supplied to sites manually outside of IXRS

system. Drug dispensation and reconciliation will be handled by site on each patient's visit. It may be necessary for the patient to move to a new study to continue treatment, in which case they will be asked to sign a new consent form. If the study drug(s) become approved on the market for use in the specific disease under study, patients may be discontinued and switched to the marketed product. Drug supply options can be available depending on the country and such situations can be discussed between AZ and the Investigator.

Revised text:
After the final analysis, AstraZeneca will continue to supply open-label drug to patients who are eligible to receive tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy (initial or repeat) (see Section 7.2). The clinical study database will be closed and only SAEs will be reported to AstraZeneca as detailed in Section 6.3.12. ~~Assessments will revert to the Investigator's standard of care. I t is recommended that Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with investigational product in order to manage AEs in accordance with the toxicity management guidelines (Appendix E and Section 6.8.1). Study drug will be supplied to sites manually outside of IXRS system. Drug dispensation and reconciliation will be handled by site on each patient's visit. It may be necessary for the patient to move to a new study to continue treatment, in which case they will be asked to sign a new consent form. If the study drug(s) become approved on the market for use in the specific disease under study, patients may be discontinued and switched to the marketed product. Drug supply options can be available depending on the country and such situations can be discussed between AZ and the Investigator.~~

Reason for Amendment:

Deleted some wording as the treatment option after final DCO clarified in section 7.2.3.

5. Section of protocol affected:

8.5 Methods for statistical analyses

Previous text:
The primary statistical analyses will be based on a minimax Simon 2-Stage design (Simon 1989) algorithm described under Section 8.2. The data cut-off for the primary analysis of all study endpoints including OS will take place approximately 12 months after the last patient completes 12 months of initial Treme monotherapy, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor.

Revised text:

The primary statistical analyses will be based on a minimax Simon 2-Stage design (Simon 1989) algorithm described under Section 8.2. The data cut-off for the primary analysis of all study endpoints including OS will take place approximately 12 months after the last patient completes 12 months of initial Treme monotherapy, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor. A final data cut-off of OS and safety will be conducted approximately 6 months after the primary analysis data cut-off.

Reason for Amendment:

To update the final DCO of OS and safety after primary analysis data cut-off.