
Clinical Study Protocol

Drug Substance	Durvalumab (MEDI4736) and tremelimumab
Study Code	D419AC00001
Version	08
Date	09 January 2018

A Phase III Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 in Combination with Tremelimumab Therapy or MEDI4736 Monotherapy Versus Standard of Care Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic Non-Small-Cell Lung Cancer (NSCLC) (MYSTIC)

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EudraCT Number: 2015-001279-39

VERSION HISTORY

Version 8.0, 9 January 2018

Changes to the protocol are summarised below.

Synopsis, Sections 6.1.9, 7.2.2

Updated to include further clarification on post final Data Cut Off (DCO) procedures.

Section 1.3.2, Potential Risks

Since the MYSTIC study was started, the durvalumab programme has developed and the emerging safety profile has become more established. As such, the “Potential Risks” section of this clinical study protocol has updated to align and be consistent with the broader durvalumab programme, including the Investigator Brochure and the clinical study protocol format of more recent studies.

Section 3.10.3, Survival Status for Withdrawn Consent and Lost to Follow Up Patients

Updated to clarify which analysis sets require survival status data and how and when to obtain this data.

Sections 6.3.1, Time period for collection of adverse events, 6.3.2, Follow-up of unresolved adverse events

Updated to clarify time period for collection of adverse events, and to clarify the follow-up of adverse events unresolved at the patient’s last visit in the study or at study completion.

6.7, Management of Investigational Product-related Toxicities

Updated to include the web link to the most current Toxicity Management Guidelines.

6.7.1, MEDI4736 + tremelimumab and MEDI4736 monotherapy adverse events of special interest (AESI)

Updated to align with the most current Investigator Brochure

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Various

Updated terminology from immune related Adverse Event (irAE) to immune mediated Adverse Event (imAE).

Version 7.0, 20 December 2016

Changes to the protocol are summarised below.

Synopsis, Section 1.4

Clarification of the expected proportion of patients with $\geq 25\%$ PD-L1 membrane-expression in tumoral tissue. With the study fully recruited there is no change in the overall patient number.

Synopsis, Glossary, Figure 1, Section 1.4

The definitions for the PD-L1 tumor membrane-expression sub-groups are provided.

Synopsis, Sections 1.1.5, 1.2.6, 1.3.1.1, 1.3.1.3, 2.1, 2.2, 2.3

For MEDI4733 in combination with tremelimumab the assessment of progression-free survival (PFS) and overall survival (OS) were nominated as co-primary objectives in NSCLC patients with $\geq 25\%$ PD-L1 membrane-expression in tumoral tissue.

For MEDI4733 monotherapy the assessment of overall survival (OS) is nominated as a co-primary objective in NSCLC patients with $\geq 25\%$ PD-L1 membrane-expression in tumoral tissue .

Primary and secondary objectives, endpoints and rationale for endpoints were modified accordingly.

Synopsis, Section 8, Table 9, Table 12, Figure 5

The statistical considerations and analyses have been updated to accommodate the nominated co-primary objectives.

Section 3.1, Inclusion Criteria #3

Correction of spelling error.

Section 4

Removed the set duration for treatment periods as they can be variable per protocol.

Table 2

Footnote O updated for clarity.

Table 4

Footnote J updated for clarity.

Sections 6.7.1, 6.7.2

Updated to align with the current IB and ICF.

Section 7.7

In the section on prohibited medications, the following changes have been made:

- A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of the patient (eg, for chronic obstructive pulmonary disease, radiation, nausea, etc).
- EGFR TKIs should not be given concomitantly whilst the patient is on study treatment. In addition they should be used with caution in the 90 days after the last dose of durvalumab. (Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased

Version 7.0, 20 December 2016

Changes to the protocol are summarised below.

incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly).

- Inactivated viruses, such as those in the influenza vaccine, are permitted

Section 8.4.4 – 8.4.4.3

Statement that the clinical meaningfulness threshold of the PRO analyses will be described in the Statistical Analysis Plan (SAP)

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Version 6.0, 02 June 2016

Changes to the protocol are summarised below.

Section 3.8 Restrictions

Spermicide was removed as it is not a highly effective method of contraception.

Synopsis, Section 7.2.2 Duration of treatment and criteria for retreatment

To clarify that treatment through progression only applies to the immunotherapy groups (monotherapy and combination therapy arms).

Updated wording in section 7.2.2. to match synopsis, indicating patients in the immunotherapy groups (rather than only the MEDI4736 group) will not be permitted to continue immunotherapy if progression occurs in a target lesion that has previously shown a confirmed response.

Section 8.4.1.1 Progression-free survival To clarify that in the SoC group treatment can be continued, at investigator's discretion, until disease progression is confirmed. Patients in the SoC are not allowed to continue treatment once disease progression is confirmed

Version 5.0, 31 March 2016

Changes to the protocol are summarized below

Title pages

MEDI4736 is identified as Durvalumab in Drug substance in the header box, and referred to as MEDI4736 thereafter.

Synopsis, Section 1.2.6 – Rationale for Endpoints, Section 2 – Study Objectives, Section 5.1 – Efficacy Assessments, Section 8.4 – Outcome Measures for Analysis, Section 8.5 – Methods for Statistical Analysis

The primary and secondary objective endpoints have been updated to reflect changes to endpoint measures - Blinded Independent Central Review (BICR) tumor assessments rather than Investigator assessments as well as to assess the treatment benefit and efficacy of MEDI4736 as suggested by emerging immuno-oncology data. Investigator assessments will be used for sensitivity analysis.

Synopsis, Section 1.4 – Study design and Section 8.2 – Sample size estimate

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Synopsis, Section 1.4 – Study design

The timing for patients to provide a tumor tissue sample was clarified as being the enrollment visit.

Synopsis, Section 1.4 – Study design and Section 2 – Study objectives

The assessment of progression-free survival (PFS) and overall survival (OS) were nominated as co-primary objectives. Primary and secondary objectives, endpoints and rationale for endpoints were modified accordingly.

Synopsis, Section 7.2.2 Duration of treatment and criteria for retreatment

Duration of treatment was modified so that patients in all groups can continue therapy until disease progression rather than stopping at 12 months. Emerging data from ongoing MEDI4736 studies is suggestive of some patients losing clinical benefit after they complete the 12 months of therapy.

In all groups, patients with PD (unconfirmed and confirmed) who, in the Investigator's opinion, would continue to receive benefit from their assigned treatment, and who meet the criteria for treatment in the setting of PD, may continue to receive treatment. It was also clarified that patients on MEDI4736 alone will not be permitted to continue immunotherapy, if the progression occurs after confirmed response to immunotherapy treatment within the target lesion, and if progression events occurred in the target lesions while the patient was receiving immunotherapy during the same treatment period.

Synopsis, Section 8 – Statistical methods

The statistical considerations and analyses have been updated to accommodate the new co-primary objectives and the modifications in provisions for duration of treatment and progression during treatment.

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Section 1.2.5 - Rationale of retreatment option

The rationale for the retreatment option is amended to enable patients in the MEDI4736 + tremelimumab combination group who complete 4 dosing cycles (providing clinical benefit per Investigator judgement), and subsequently have PD during treatment with MEDI4736 alone, to restart combination treatment, if they also meet eligibility criteria.

Section 1.3.2.1 - MEDI4736 + tremelimumab

The potential risks, based on the mechanism of action of MEDI4736 and related molecules, are updated to “colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with MEDI4736 and tremelimumab combination therapy. Other inflammatory responses with potential immune-mediated etiology reported with MEDI4736 and similar molecules include myocarditis, pericarditis, and uveitis” in accordance with the current Investigator Brochure.

Section 3.2 - Exclusion criteria

- Sarcomatoid variant of non-small-cell lung cancer (NSCLC) is added as an exclusion criteria.
- The part of the exclusion criteria of brain metastases or spinal cord compression and off steroids and anticonvulsants for at least 1 month prior to study treatment is amended to and off steroids for at least 14 days prior to study treatment. In addition, following radiotherapy and/or surgery, patients with brain metastases must wait 4 weeks after the intervention and must confirm stability with imaging before randomization.
- Tuberculosis (clinical evaluation) has been added to hepatitis B, hepatitis C and human immunodeficiency virus as part of the active infection exclusion criterion. The exclusion criterion Known history of clinical diagnosis of tuberculosis has been deleted. In addition supplementary information on the diagnoses are given:
 - HIV diagnosis requires positive HIV 1 or 2 antibodies.

- Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).

Section 3.8 - Restrictions

- The restrictions for female patients of childbearing potential are strengthened from 2 methods of effective contraception to at least 1 highly effective method (ie, low failure rate of <1% per year). Additionally the male partners of a female patient of child bearing potential must use a male condom plus spermicide (except in countries where spermicides are not approved).
- Male patients with a female partner of childbearing potential must use a male condom plus spermicide (except in countries where spermicides are not approved), and it is highly recommended for the female partner of a male patient to also use a highly effective method of contraception.

Section 3.9 - Discontinuation of IP

The stipulation for discontinuation of IP of any adverse event (AE) that meets the criteria for discontinuation was removed.

Section 4 – Study plan and timing of procedures

In Table 2 (Schedule of Assessments) the following amendments were:

- The window for Cycle 1 was amended from +1 to +3 days
- Activated partial thromboplastin time (APTT) and international normalized ratio (INR) assessments, which will be performed as clinically indicated and at Screening, were added to the table.
- For the pharmacokinetic samples, it is now specified that they will take place on the same day as the infusion and within 1 hour of end of infusion, as opposed to up to 1 hour predose and with 10 minutes of the end of the infusion.

Section 5.1 - Efficacy Assessments

The timing for performing the baseline assessment was modified to no more than 28 days before randomization rather than no more than 28 days before the start of IP treatment.

Section 5.1.2 - Survival assessments

Patients on treatment or in survival follow-up will now be contacted following the data cut-off for the primary analysis of the PFS and for each interim and final analysis of OS rather than following

the data cut-off for the primary analysis and all subsequent survival analyses to provide complete survival data.

Section 5.2.1 - Laboratory safety assessments

- In Table 5, provision is made that if the amylase and lipase analyses could not be performed in a local laboratory, then 1 or the other would be performed in line with local practice.
- In Table 6, APPT and INR are added to the table, and it is stipulated that they will be assessed at Screening rather than Baseline as indicated in the table footnote.

Section 5.2.4 – Vital signs

Blood pressure may now be measured in a supine or semi-supine position rather than just a supine position.

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Section 6 – Safety reporting and medical management

In accordance with the new protocol template, the following first 3 sub-sections of Section 6 were reordered **from**:

- 6.1 Definition of serious adverse events
- 6.2 Recording of adverse events
- 6.3 Definition of adverse events

to

- 6.1 Definition of adverse events
- 6.2 Definition of serious adverse events
- 6.3 Recording of adverse events

Section 6.7.1 - MEDI4736 + tremelimumab and MEDI4736 monotherapy adverse events of special interest (AESI)

This section was updated to remove the detailed explanation of MEDI4736's main AESIs and refer the reader to the current IB where these are explained in full, together with specific guidelines for their evaluation and treatment.

Section 7.1 - Identity of IP

The section for MEDI4736 and tremelimumab is updated with the current recommendations for preparation and dose calculations.

Section 7.7 – Concomitant and other treatments

In the section on prohibited medications, the following amends are made:

- Systematic corticosteroid will be permitted for the prevention of chemotherapy-related toxicities (nausea/vomiting prevention and prophylaxis)
- Drugs with laxative properties should be used with caution rather than avoided
- Herbal and natural remedies in general, rather than those for constipation only, should be avoided for 90 days after the last dose of MEDI4736 monotherapy or combination treatment (MEDI4736 + tremelimumab) during the study

Section 8.3 - Definition of analysis set

The outcome variables for the efficacy data were updated in Table 9 to align with the revised co-primary endpoints.

Section 8.4.1 – Calculation or derivation of efficacy variables

BICR of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1)-based assessments were moved above Investigator RECIST 1.1-based assessments. Text of BICR-based assessments was changed to reflect BICR-RECIST 1.1 analysis on all radiological scans of all patients rather than a random sample.

Section 8.4.1.2 – Calculation or derivation of efficacy variables and Section 8.5.2 – Objective response rate

Text was added to explain that objective response rate analysis of Investigator tumor data is based upon RECIST 1.1 as a sensitivity analysis.

Section 8.5.1.1 – Progression-free survival, and Section 11 – References

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Version 4.0, 7 August 2015

Changes to the protocol are summarised in Amendment 3.

Version 3.0, 28 July 2015

Changes to the protocol are summarised in Amendment 2.

Version 2.0, 27 May 2015

Changes to the protocol are summarised in Amendment 1.

Version 1.0, 21 April 2015

Initial document.

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This clinical study protocol has been subject 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 III Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 in Combination with Tremelimumab Therapy or MEDI4736 Monotherapy Versus Standard of Care Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic Non-Small-Cell Lung Cancer (NSCLC) (MYSTIC)

International Coordinating Investigators

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Study site(s) and number of patients planned

The study will enroll approximately 1850 patients to identify approximately 1092 patients who will be randomized to receive MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or platinum-based Standard of Care (SoC) therapy (364 in each group, including approximately 160 patients in each treatment group with programmed cell death ligand 1 [PD-L1]-positive non-small-cell lung cancer [NSCLC], defined as PD-L1 expression $\geq 25\%$).

Study period	Phase of development	
Estimated date of first patient enrolled	Q3 2015	III
Estimated date of last patient completed	Q2 2018	III

Study design

This is a randomized, open-label, multi-center, global, Phase III study to determine the efficacy and safety of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus platinum-based SoC chemotherapy in the first-line treatment of patients with epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type advanced or metastatic NSCLC.

Patients will provide a tumor tissue sample at enrollment to determine PD-L1 expression status (defined by the **CCI** in which:

- $\geq 25\%$ PD-L1 & $> 1\%$ PD-L1 membrane-expression in tumoral tissue are considered as relevant positive sub-groups
- $< 25\%$ PD-L1 is considered low/negative
- $< 1\%$ is considered negative;

For clarity these sub-groups are referred to hereafter as patients with PD-L1 positive_{25%}, PD-L1 positive_{1%}, PD-L1-low/negative or PD-L1-negative tumors, respectively.

Patients will be randomized in a 1:1:1 ratio in a stratified manner according to PD-L1 tumor expression status (PD-L1 positive_{25%} versus PD-L1-low/negative) and histology (squamous versus non-squamous) to receive treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC therapy.

Tumor assessments will be performed every 6 weeks for the first 48 weeks and then every 8 weeks until confirmed disease progression, with categorization of objective tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).

Objectives

All objectives will be evaluated for all patients, unless otherwise indicated, and where appropriate for patients with PD-L1 positive_{25%}, PD-L1 positive_{1%}, PD-L1-low/negative and/or PD-L1-negative NSCLC. The assessment of progression-free survival (PFS) and overall survival (OS) in patients with PD-L1 positive_{25%} NSCLC will be considered the co-primary objectives.

Primary Objective:	Outcome Measure:
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS in patients with PD-L1 positive _{25%} NSCLC	PFS using Blinded Independent Central Review (BICR) assessments according to RECIST 1.1
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC terms of OS in patients with PD-L1 positive _{25%} NSCLC	OS
To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of OS in patients with PD-L1 positive _{25%} NSCLC	OS

Secondary Objectives:	Outcome Measures:
<p>To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS, OS, objective response rate (ORR), duration of response (DoR), proportion of patients alive and progression free at 12 months from randomization (APF12), and time to second progression (PFS2)</p>	<p>OS in PD-L1 positive_{1%} patients and all patients PFS in PD-L1 positive_{1%} patients and all patients using BICR assessments according to RECIST 1.1 ORR, DoR, and APF12 in patients with PD-L1 positive_{25%} NSCLC, and patients with PD-L1 positive_{1%} NSCLC and all patients using BICR assessments according to RECIST 1.1 PFS2 in patients with PD-L1 positive_{25%} NSCLC, and patients with PD-L1 positive_{1%} NSCLC and all patients using local standard clinical practice^a</p>
<p>To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of PFS, ORR, DoR, APF12, and PFS2</p>	<p>PFS in patients with PD-L1 positive_{25%} NSCLC using BICR assessments according to RECIST 1.1 ORR, DoR, and APF12 in patients with PD-L1 positive_{25%} NSCLC using BICR assessments according to RECIST 1.1 PFS2 in patients with PD-L1 positive_{25%} NSCLC using local standard clinical practice^a</p>
<p>To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, OS, and ORR</p>	<p>PFS and ORR in patients with PD-L1 positive_{25%} and PD-L1 positive_{1%} NSCLC and all patients using BICR assessments according to RECIST 1.1 OS in patients with PD-L1 positive_{25%} and PD-L1 positive_{1%} NSCLC and all patients</p>
<p>To assess disease-related symptoms and health-related quality of life (HRQoL) in patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC using the EORTC 30-item core quality of life questionnaire, Version 3 (QLQ-C30 v3) and the 13-item lung cancer quality of life questionnaire (QLQ-LC13) module</p>	<p>EORTC QLQ-C30 EORTC QLQ-LC13 Changes in World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status will also be assessed.</p>
<p>To assess the pharmacokinetics (PK) of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy</p>	<p>Concentration of MEDI4736 and tremelimumab in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling)</p>

Secondary Objectives:	Outcome Measures:
To investigate the immunogenicity of MEDI4736 and tremelimumab	Presence of anti-drug antibodies (ADAs) for MEDI4736 and tremelimumab

^a PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death, based on Investigator tumor assessments.

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC in the first-line setting for treatment of advanced or metastatic patients with NSCLC	Adverse events (AEs), physical examinations, laboratory findings, and vital signs

Target patient population

Adult patients (age ≥ 18 years) with advanced or metastatic (Stage IV) histologically or cytologically documented EGFR and ALK wild-type NSCLC who are treatment naive.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients in all groups will continue therapy until disease progression.

Progression during treatment

Patients in all groups may continue receiving therapy in the setting of unconfirmed progressive disease (PD) until PD is confirmed, at the Investigator's discretion. According to RECIST 1.1, modified for confirmation of progression, a confirmatory scan will be required following an overall time-point assessment of progression, preferably at the next scheduled visit, and no earlier than 4 weeks after the previous assessment of PD.

Patients in all groups, excluding the SoC arm, with PD according to RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, would continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD, may continue to receive their assigned treatment for as long as they are still gaining clinical benefit. However, patients in the immunotherapy group(s) will not be permitted to continue immunotherapy if progression occurs after confirmed response (CR, defined by RECIST 1.1) to immunotherapy treatment in the target lesions, ie, the response and progression events both occurred in the target lesions while the patient was receiving immunotherapy during the same treatment period.

Patients in the MEDI4736 + tremelimumab group may restart treatment with the combination therapy if they complete the 4 dosing cycles with MEDI4736 + tremelimumab (with clinical

benefit per Investigator judgment) but subsequently have PD during treatment with MEDI4736 alone and if they meet eligibility criteria for retreatment.

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive durvalumab treatment 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 durvalumab in order to manage AEs in accordance with the durvalumab toxicity management guidelines (please see [Section 6.1.9](#)).

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 durvalumab 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 visits assessment per its protocol. Any patient that would be proposed to move to such study would be given a new Informed Consent.

Investigational product, dosage, and mode of administration

MEDI4736 + tremelimumab combination therapy

- MEDI4736 20 mg/kg via IV infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 doses/cycles, and then continue MEDI4736 20 mg/kg via IV infusion q4w, starting on Week 16
- Tremelimumab 1 mg/kg via IV infusion q4w, starting on Week 0, for up to 4 doses/cycles

MEDI4736 monotherapy

- MEDI4736 20 mg/kg via IV infusion q4w, starting on Week 0

Standard of Care therapy

Patients randomized to SoC therapy will receive 1 of the following:

- Paclitaxel + carboplatin: Paclitaxel 200 mg/m² and carboplatin area under the curve (AUC) 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m² via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m² via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m² via IV infusion on Days 1 and 8 of each 21-day cycle +

carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD

- Pemetrexed + cisplatin (non-squamous patients only): Pemetrexed 500 mg/m² and cisplatin 75 mg/m² via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy.
- Pemetrexed + carboplatin (non-squamous patients only): Pemetrexed 500 mg/m² and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy.

Statistical methods

The primary objectives of this study are to assess the efficacy of MEDI4736 + tremelimumab treatment compared with SoC in terms of PFS and OS and of MEDI4736 monotherapy compared with SoC in terms of OS in patients with EGFR and ALK wild-type advanced or metastatic NSCLC with PD-L1 positive_{25%} tumors. PFS (per RECIST 1.1, using BICR tumor assessments) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression. OS will be defined as the time from the date of randomization until death due to any cause. Thus, primary endpoints in this study are PFS and OS, in patients with PD-L1 positive_{25%} NSCLC. To control for type I error, an alpha of 0.03 will be used for the OS comparison of MEDI4736 monotherapy versus SoC, an alpha of 0.015 will be used for the OS comparison of MEDI4736 + tremelimumab versus SoC and an alpha of 0.005 will be used for the PFS comparison of MEDI4736 + tremelimumab versus SoC. The study will be considered positive (a success) if any of the OS or PFS analysis results are statistically significant.

Secondary efficacy variables include PFS and OS for MEDI4736 + tremelimumab versus SoC in patients with PD-L1 positive_{1%}, and all randomized patients, PFS for MEDI4736 monotherapy versus SoC in patients with PD-L1 positive_{25%} tumours, and PFS and OS for MEDI4736+tremelimumab versus MEDI4736 monotherapy in patients with PD-L1 positive_{25%} and PD-L1 positive_{1%} tumors and all randomized patients, as well as ORR, DoR, APF12, and PFS2. All tumor-assessment-related endpoints are as assessed by BICR

Efficacy data will be summarized and analyzed on an intent-to-treat (ITT) basis and the treatment groups will be compared on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

Approximately 1092 patients (including approximately 160 patients per arm with PD-L1 positive_{25%} NSCLC) will be randomized 1:1:1 to MEDI4736 + tremelimumab, MEDI4736 monotherapy, or SoC. The randomization will be stratified based on PD-L1 tumor expression status ($\geq 25\%$ versus $< 25\%$) and histology (squamous versus non-squamous). The primary PFS

analysis for superiority will be performed when both of the following conditions have been met:

- Approximately 231 BICR PFS events have occurred across the MEDI4736 + tremelimumab and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (72% maturity) AND
- CCI [REDACTED] to the study

The final (primary) OS analysis for superiority will be performed when the following conditions have been met:

- Approximately 225 OS events have occurred across the MEDI4736 + tremelimumab and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (70% maturity) AND
- Approximately 225 OS events have occurred across the MEDI4736 monotherapy and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (70% maturity)

Two interim analyses to assess the superiority of the MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy group (compared to the SoC group) in terms of OS will be performed at the time of the primary PFS analysis, and when approximately 80% of the target OS events have been reached, respectively.

MEDI4736 + tremelimumab versus SoC (PFS in PD-L1 positive_{25%} population)

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MEDI4736 + tremelimumab versus SoC (OS in PD-L1 positive_{25%} population)

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MEDI4736 monotherapy versus SoC (OS in PD-L1 positive_{25%} population)

CCI [REDACTED]

CCI



PFS, based on the programmatically derived PFS from BICR, and OS will be analyzed using a stratified log-rank test. The stratification will be by histology alone (squamous, non-squamous) for the primary comparisons using the PD-L1 positive_{≥25%} population, and will be by PD-L1 tumor expression status ($\geq 25\%$, $< 25\%$) and histology for the secondary analyses using the PD-L1 positive_{≥1%} population and full ITT population. The effect of treatment will be estimated by the HR together with corresponding two-sided appropriately sized CI, (adjusted for interim analyses) and p-value.

Safety data will be summarized descriptively and formal statistical comparisons will not be made.


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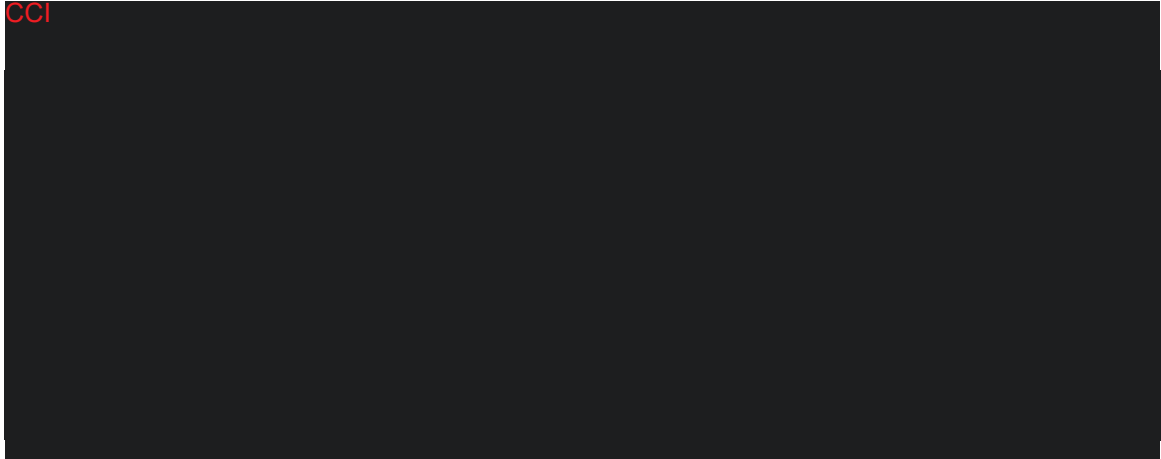
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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 events of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time;
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUC _{ss}	Area under the curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
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
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
C _{trough,ss}	Trough plasma concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
CCI	
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
IMT	Immunomodulatory therapy

Abbreviation or special term	Explanation
INR	International normalized ratio
IP	Investigational product
imAE	Immune-mediated adverse event
IRB	Internal Review Board
irRECIST 1.1	Immune-related response criteria, Version 1.1
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L1 positive _{25%}	≥25% of tumor cells with membrane staining for PD-L1 at any intensity
PD-L1-positive _{1%}	≥1% of tumor cells with membrane staining for PD-L1 at any intensity
PD-L1-low/negative	<25% of tumor cells with membrane staining for PD-L1 at any intensity
PD-L1-negative	<1% of tumor cells with membrane staining for PD-L1 at any intensity
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival

Abbreviation or special term	Explanation
PFS2	Time to second progression
CCI	
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
CCI	
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
QLQ-C30 v3	30-item core quality of life questionnaire, Version 3
QLQ-LC13	13-item lung cancer quality of life questionnaire
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
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T ₃	Triiodothyronine
T ₄	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

Abbreviation or special term	Explanation
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Lung cancer has been the most common cancer in the world for several decades, with an estimated 1.8 million new cases in 2012 (12.9% of all new cancers), and was also the most common cause of death from cancer in 2012, with 1.59 million deaths (19.4% of the total cancer deaths; [GLOBOCAN 2012](#)). Non-small-cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis, approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of patients with early stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer ([Pisters and LeChevalier 2005](#)).

Despite advances in the diagnosis, imaging, staging, and treatment of NSCLC, the estimated overall 5-year survival for patients in Europe and the United States (US) continues to be low (11% and 17%, respectively; [D'Addario et al 2010](#), [Howlander et al 2014](#)). Patients presenting with advanced NSCLC have a median overall survival (OS) of 10 to 12 months ([Bonomi 2010](#)). Patients without a targetable mutation (ie, epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] mutation) demonstrate responses to systemic treatment of approximately 20% to 30% and progression-free survival (PFS) of 4 to 5 months ([Scagliotti et al 2008](#), [Schiller et al 2002](#)). The durations of responses (DoRs) are also limited, and toxicities can be a major limiting factor. The 1-year survival rate is 30% to 40% for patients with a good performance status. Maintenance therapy, with either continuation or switch, has also been recommended for certain histologic subtypes of NSCLC; for example, maintenance with pemetrexed has been shown to improve OS and PFS, particularly in non-squamous histologies ([Ciuleanu et al 2009](#), [Paz-Ares et al 2013](#)).

Common first-line treatment regimens for advanced NSCLC in major global markets are typically platinum-based doublets and include carboplatin and paclitaxel, carboplatin and gemcitabine (squamous only), carboplatin and pemetrexed (non-squamous only), cisplatin and gemcitabine (squamous only), and cisplatin and pemetrexed (non-squamous only). Platinum-based doublet chemotherapy regimens vary to some extent with regard to convenience, associated toxicities, and cost, with the selection of a specific regimen often dictated by local practice and individualized on a case-by-case basis.

1.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors ([Dunn et al 2004](#)). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors ([Peggs et al 2009](#)). This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-H1 programmed cell death ligand 1 [PD-L1]).

1.1.2 MEDI4736

MEDI4736 is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As MEDI4736 is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1.

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of patients with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of patients with tumors lacking PD-L1 (Mu et al 2011). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of several non-clinical studies using mouse tumor models support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity (Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Zhang et al 2008).

MEDI4736 has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of 14 July 2014, 509 patients have been enrolled and treated in 10 ongoing clinical studies of MEDI4736 (5 employing MEDI4736 as monotherapy and 5 as combination therapy). Details on the safety profile of MEDI4736 monotherapy are summarized in Section 1.3.2.1. Refer to CCI for a complete summary of non-clinical and clinical information and guidance on management of MEDI4736-related toxicities.

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

1.1.3 Tremelimumab

Tremelimumab, a CTLA-4 mAb of the IgG 2 kappa isotype, is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer. Tremelimumab is a human IgG2 mAb directed against CTLA-4.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood

or peripheral blood mononuclear cell (PBMC) cultures (Tarhini and Kirkwood 2008). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. (Refer to the current version of the tremelimumab investigator brochure [IB] for more information.) Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cut-off date of 12 November 2014 (for all studies except D4190C00006, which has a cut-off date of 4 December 2014), 973 patients have received tremelimumab monotherapy (not including 497 patients who have been treated in the blinded Phase 2b study, D4880C00003) and 208 patients have received tremelimumab in combination with other agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.3. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information and see CCI for guidance on management of tremelimumab-related toxicities.

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

1.1.4 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 anti-tumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is MEDI4736 every 2 or 4 weeks (q2w; q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks (q12w) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

As of 27 January 2015, a total of 74 patients have been treated in the study, including 58 patients on the q4w dosing schedule and 16 patients on the q2w dosing schedule. Patients have received between 1 and 13 doses of MEDI4736 and between 1 and 9 doses of tremelimumab. Details on the safety profile of MEDI4736 + tremelimumab combination therapy are summarized in Sections 1.2.1 and 1.3.2.4. Refer to the current versions of the MEDI4736 IB and the tremelimumab IB for a complete summary of non-clinical and clinical information and CCI for guidance on management of MEDI4736 + tremelimumab-related toxicities.

As of 27 January 2015 in Study D4190C00006, an approximately dose-proportional increase in PK exposure (maximum plasma concentration [C_{max}] and area under the plasma drug concentration-time curve (AUC) from time zero to Day 28 post-dose) 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 with ADA data available 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 programmed cell death ligand 1 (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

Current therapies for advanced NSCLC have poor outcomes (low 5-year survival of 17% for the US), with responses to systemic chemotherapy in the first-line setting of approximately 20% to 30%, and a median OS of approximately 10 to 12 months (Bonomi 2010, D'Addario et al 2010, Scagliotti et al 2008, Schiller et al 2002). Responses are also limited in duration. Systemic chemotherapy is associated with significant side effects, including neutropenia, nausea, vomiting and dehydration, and alopecia (Sandler et al 2006, Scagliotti et al 2008). There is still a significant unmet medical need for additional treatment options for use in this patient population as the 1-year survival rate is 30% to 40%.

As an antibody that blocks the interaction between PD-L1 and its receptors, MEDI4736 may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile (Brahmer et al 2012, Topalian et al 2012). Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In addition, MEDI4736 monotherapy has shown durable responses in NSCLC in Study 1108 (see Section 1.3.1.1).

The rationale for combining MEDI4736 and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity (Pardoll 2012). In fact, combining immunotherapy agents has been shown to result in improved response rates relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable (Wolchok et al 2013). Similar results have been observed in an ongoing study of MEDI4736 + tremelimumab in NSCLC (Antonia et al 2014a), with further updated details presented in this clinical study protocol.

Based on the preliminary clinical efficacy and safety data observed in patients with NSCLC in Study D4190C00006 (with MEDI4736 + tremelimumab) and in Study 1108 (with MEDI4736 monotherapy), AstraZeneca plans to determine the activity of MEDI4736 in combination with tremelimumab and MEDI4736 monotherapy as first-line treatment in patients with NSCLC. The preliminary efficacy, safety, and tolerability data of the MEDI4736 + tremelimumab combination in Study D4190C00006 and MEDI4736 monotherapy in Study 1108 support the

development of these treatments in NSCLC. The primary endpoints of this Phase III study are to determine the activity of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to Standard of Care (SoC) in patients with EGFR and ALK wild-type NSCLC when used as first-line treatment in patients with PD-L1 positive_{25%} tumors and secondary endpoints will include the comparison of the activity in patients with PD-L1 positive_{1%} tumours and all randomised patients. In addition to quantifying the clinical effects of MEDI4736 in combination with tremelimumab, this will also allow comparison between the relative efficacy and tolerability of MEDI4736 + tremelimumab and MEDI4736 alone.

1.2 Rationale for study design, doses, and control groups

This study will utilize an open-label design due to the different treatment administration schedules and treatment durations.

1.2.1 MEDI4736 + tremelimumab combination therapy dose rationale

The MEDI4736 + tremelimumab 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.

As of 27 January 2015, a total of 74 patients with advanced NSCLC have been treated in Study D4190C00006. The 74 patients have received between 1 and 9 doses of tremelimumab and between 1 and 13 doses of MEDI4736. 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. Fifty-eight of these patients were in the q4w dosing schedule and 16 patients were in the q2w dosing schedule, with the goal of identifying the dose combination that best optimizes the risk:benefit profile in an acceptable range of PK and pharmacodynamic values.

In order to reduce the dosing frequency of MEDI4736 to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/pharmacodynamic, safety, and efficacy profile, cohorts were narrowed to 15 and 20 mg/kg MEDI4736 q4w. PK simulations from the MEDI4736 monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss} ; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w MEDI4736. The observed MEDI4736 PK data from the D4190C00006 study 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} at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in 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 plus 1 mg/kg tremelimumab combinations.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab and 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohort than the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with 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 rate 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-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of MEDI4736.

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥ 3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥ 3 AEs or treatment related SAEs. No dose-limiting toxicities (DLTs) were reported.

Preliminary clinical activity of the MEDI4736 and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg MEDI4736 q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR), 1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD). (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Additionally, of all cohorts, the 20 mg/kg 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 MEDI4736 + 1 mg/kg tremelimumab dose combination should be selected for further development.

1.2.2 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 every 3 weeks 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 ([Hodi et al 2014](#), [Brahmer et al 2014](#), [Drake et al 2013](#)). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis ([Topalian et al 2014](#)).
- MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported ([Herbst et al 2013](#), [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 combination of the two.

The MEDI4736 + tremelimumab combination regimen will be administered for 4 doses followed by monotherapy MEDI4736 20 mg/kg q4w.

1.2.3 MEDI4736 monotherapy dose rationale

A dose of MEDI4736 dose of 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).

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 cut-off of 21 August 2014 showed that MEDI4736 was well tolerated at all doses in the NSCLC subset of patients 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, no Grade ≥ 3 pneumonitis reported, and no drug-related AEs leading to death were reported ([Antonia et al 2014b](#)). No DLTs were observed up to a dose of 10 mg/kg q2w or 15 mg/kg every 3 weeks (q3w).

Efficacy data on the patients with NSCLC in Study 1108, presented at ESMO 2014 (cut-off date of 21 August 2014), showed a disease control rate (DCR) at 12 weeks of 41% and 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 $\geq 25\%$ 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 2014b](#)).

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 were ADA positive, with an impact on PK/pharmacodynamics reported in 1 patient at 3 mg/kg.

Data from Study 006 (Phase I trial in patients with NSCLC 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. The observed MEDI4736 PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a q4w regimen.

A population PK model was developed using the data from Study 1108 (doses=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_{ss} ; 4 weeks. 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). 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, pharmacodynamic, 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 anti-tumor activity in animal models.

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 q2w regimen, and there were no DLTs observed. Of the 12 patients in Study 1108, 42% of patients have experienced any grade AE, with 2 being Grade 3 and above (17%). None of the Grade 3 and higher events was considered treatment-related. No patients on the Japan Phase I trial have experienced a Grade 3 or above AE. 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 regimen.

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.

1.2.4 Rationale for Standard of Care as a comparator

The choice of SoC options provided in this study includes carboplatin and paclitaxel, carboplatin (or cisplatin) and gemcitabine (squamous only), carboplatin (or cisplatin) and pemetrexed (non-squamous only), and for eligible patients, pemetrexed maintenance (non-squamous only). Patients in the SoC group will receive treatment determined by the Investigator, from the SoC agents approved for use in NSCLC in their local market, until progression per standard practice. The SoC options provided in this study include agents that are commonly used in advanced or metastatic NSCLC and allow sufficient flexibility for Investigators and patients to select the agents that reflect their normal clinical practice and national guidelines ([NCCN 2014](#) and [Reck et al 2014](#)).

1.2.5 Rationale for retreatment option

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 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 2014](#); [Hodi et al 2010](#)).

Patients in the MEDI4736 + tremelimumab group who complete 4 dosing cycles (with clinical benefit per Investigator judgement), and subsequently have PD during treatment with MEDI4736 alone may restart treatment if they meet eligibility criteria for retreatment.

1.2.6 Rationale for endpoints

The primary objectives of this study are to assess the efficacy of:

- MEDI4736 + tremelimumab treatment compared with SoC in terms of PFS in patients with EGFR and ALK wild-type advanced or metastatic NSCLC with PD-L1 positive_{25%} tumors
- MEDI4736 + tremelimumab treatment compared with SoC in terms of OS in patients with EGFR and ALK wild-type advanced or metastatic NSCLC with PD-L1 positive_{25%} tumors
- MEDI4736 treatment compared with SoC in terms of OS in patients with EGFR and ALK wild-type advanced or metastatic NSCLC with PD-L1 positive_{25%} tumors

Within the statistical hierarchy, a key secondary endpoint of the study is to assess the efficacy in the overall study population:

- MEDI4736 + tremelimumab treatment compared with SoC in terms of PFS and OS in patients with EGFR and ALK wild-type advanced or metastatic NSCLC with PD-L1 positive_{1%} tumors and in the overall NSCLC population

Emerging data in immuno-oncology suggest that the treatment benefit of immunotherapies can more strongly manifest in OS compared to PFS ([Borghaei et al 2015](#), [Brahmer et al 2015](#), [Fehrenbacher et al 2016](#)), and therefore, both PFS and OS are co-primary endpoints. Additionally, the emerging immuno-oncology data indicate an improved treatment effect in patients with NSCLC tumors that express PD-L1 for both combination and monotherapy ([Hellman et al 2016](#), [Reck et al 2016](#)). Therefore, the study characterizes the efficacy of MEDI4736 + tremelimumab and MEDI4736 monotherapy in the treatment in the PD-L1-positive NSCLC population ($\geq 25%$, $\geq 1%$) and in the overall NSCLC population.

The secondary efficacy endpoints of ORR, DoR, proportion of patients alive and progression-free and time to second progression (PFS2) will be examined to further evaluate the anti-tumor effect and survival benefit of MEDI4736 + tremelimumab versus SoC. The secondary efficacy endpoints of PFS, ORR and PFS2 will also be examined to further evaluate the anti-tumor effect and survival benefit of MEDI4736 monotherapy compared to SoC. PFS and ORR will be examined to further evaluate the anti-tumor effect of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy. ORR and DoR will be assessed using Blinded Independent Central Review (BICR) assessments according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).

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The secondary health-related quality of life (HRQoL) assessments (the European Organisation for Research and Treatment of Cancer [EORTC] 30-item core quality of life questionnaire,

Version 3 [QLQ-C30 v3] and 13-item lung cancer quality of life questionnaire [QLQ-LC13]) will show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and will aid in understanding of the benefit/risk evaluation. These patient-reported outcome (PRO) questionnaires are well-established instruments that have been previously included in lung cancer clinical trials.

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1.3 Benefit/risk and ethical assessment

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

1.3.1 Potential benefits

1.3.1.1 MEDI4736

The majority of the safety and efficacy data currently available for MEDI4736 are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Data from Study 1108 were presented at the ESMO 2014 Congress. As of 21 August 2014, 162 patients with NSCLC were evaluable for response analysis. The DCR at 12 weeks in patients receiving 10 mg/kg MEDI4736 q2w was 39%, and the ORR was 15% (26% [12 out of 47 patients] with known PD-L1-positive NSCLC [ie, $\geq 25\%$ PD-L1 expression] and 10% [7 out of 74 patients] with known PD-L1 low/negative NSCLC [ie, $< 25\%$ PD-L1 expression]). A total of 24% of patients receiving 10 mg/kg MEDI4736 q2w had SD for ≥ 12 weeks (including 21% [10 out of 47 patients] with known PD-L1-positive NSCLC and 32% [24 out of 74 patients] with known PD-L1-negative NSCLC). Responses were ongoing in 88% of patients with NSCLC, with an objective response duration ranging from 0.1 to 32.4 weeks ([Antonia et al 2014b](#)).

1.3.1.2 Tremelimumab

In a single-group, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, a response rate (RR) of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis, [Korn et al 2008](#)) were observed ([Kirkwood et al 2010](#)). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed an RR of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant ([Ribas et al 2013](#)). Additionally, a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who had responded or remained stable failed to

achieve statistical significance. The primary endpoint of PFS at 3 months was 22.7% in the tremelimumab group (15 mg/kg) compared with 11.9% in the best supportive care group (Study A3671015).

1.3.1.3 MEDI4736 + tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.2.1 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). Further, preliminary efficacy data from Study D4190C00006 has demonstrated that this combination is clinically active and well tolerated. As of 27 January 2015, 53 patients were evaluable for response across various MEDI4736 + tremelimumab dose regimens. Of these, 12 patients (23%) had a best response of PR and 14 patients (26%) had a best response of SD. In the MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg q4w cohort, a total of 5 of 11 patients were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with PR, 1 patient (20%) with SD, and 1 patient (20%) with PD. (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

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

Data from ongoing studies with MEDI4736 and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (eg, NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious (in terms of ORR) in patients who are PD-L1-positive.

Given the findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1-positive tumors. Though biomarker development is ongoing, and the final boundaries of these populations are yet to be established, there is also an unmet medical need in patients with PD-L1-low/negative tumors that needs to be addressed. Data, as of 27 January 2015 from Study 006 show that with the addition of tremelimumab to MEDI4736, the ORR can be increased to 25% in patients with PD-L1-low/negative NSCLC (as defined by the CCI [REDACTED]). As patients with PD-L1 positive ($\geq 25\%$) tumors can also have an increase in ORR, from 25% with MEDI4736 monotherapy, to 36% with the combination of MEDI4736 and tremelimumab, the study will enroll all patients with NSCLC, with efficacy analysis performed in the overall study population, and pre-defined PD-L1 subgroups.

1.3.2 Potential risks

1.3.2.1 Overall 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.

1.3.2.2 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 ($\geq 10\%$ 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 Section 6.7.2).

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

1.3.2.3 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.

Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly ($\geq 10\%$ of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnoea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

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

1.3.2.4 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 ($\geq 10\%$ 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-risk and ethical assessment

There remains a significant unmet medical need for additional treatment options for patients with EGFR and ALK wild-type, advanced or metastatic NSCLC who have not received prior chemotherapy or any systemic therapy for advanced or metastatic NSCLC.

The study design aims to minimize potential risks; intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with the IPs (ie, MEDI4736 + tremelimumab, MEDI4736, and SoC).

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 MEDI4736 in this tumor type, and the strength of the scientific hypotheses under evaluation, the MEDI4736 + tremelimumab combination and the MEDI4736 monotherapy treatments proposed for evaluation in this study may have the potential to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable clinical responses, thereby improving quality of life (QoL) and potentially extending survival.

Therefore, the investigation of the potential therapeutic efficacy of the combination of MEDI4736 with tremelimumab and MEDI4736 monotherapy in patients with PD-L1-positive and -negative tumors is acceptable, and the overall benefit/risk assessment supports the proposed study design.

1.4 Study design

This is a randomized, open-label, multi-center, global Phase III study to determine the efficacy and safety of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus platinum-based SoC chemotherapy in the first-line treatment of patients with EGFR and ALK wild-type advanced or metastatic NSCLC. A schematic diagram of the overall study design is shown in [Figure 1](#), and a detailed study flow chart is shown in [Figure 2](#).

This study will enroll approximately 1850 patients at sites in North America, Asia, Australia, and Europe to randomize approximately 1092 patients (including approximately 160 patients with PD-L1 positive_{25%} NSCLC in each treatment group) to treatment.

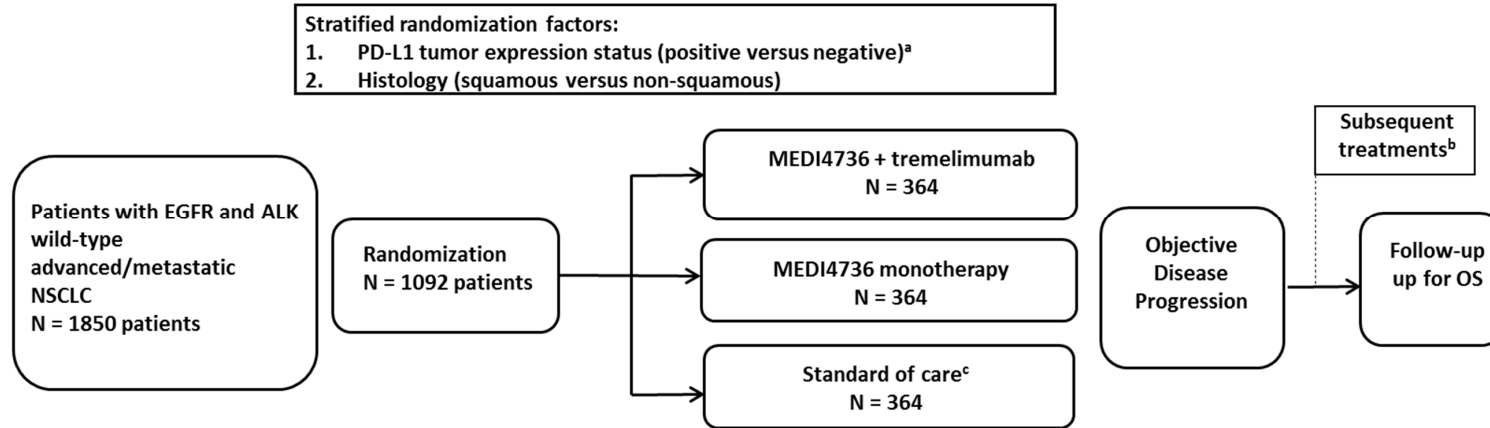
Patients will provide a tumor tissue sample at enrollment (newly acquired or archived sample <3 months old) to determine PD-L1 expression status at 25% (defined by the ^{CCI} [REDACTED] [REDACTED] in which:

- $\geq 25\%$ PD-L1 & $> 1\%$ PD-L1 membrane-expression in tumoral tissue are considered as relevant positive sub-groups
- $< 25\%$ PD-L1 is considered low/negative
- $< 1\%$ is considered negative;

Patients will be randomized in a 1:1:1 ratio in a stratified manner according to PD-L1 tumor expression status (PD-L1 positive_{25%} versus PD-L1-low/negative) and histology (squamous versus non-squamous) to receive treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC therapy.

Doses and treatment regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 2, Table 3, and Table 4.

Figure 1 Overall study design

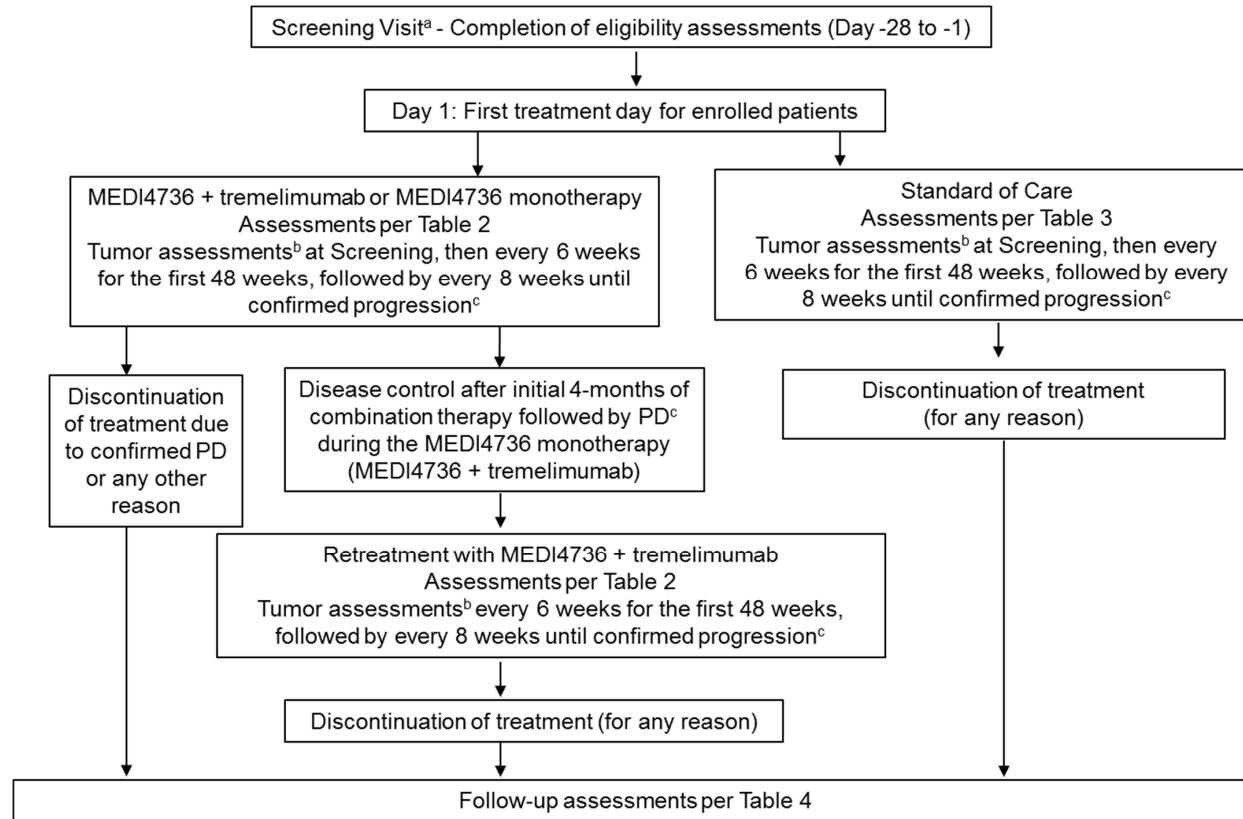


^a Stratification by PD-L1 membrane-expression in tumoral tissue ($\geq 25\%$, $< 25\%$). Sites will be supplied with PD-L1 status upon request at disease progression.

^b Offer of standard chemotherapy per Investigator discretion.

^c Standard of Care is an Investigator choice from the following: paclitaxel + carboplatin, gemcitabine + cisplatin (or carboplatin) (squamous only), pemetrexed + cisplatin (or carboplatin) (non-squamous only), and for eligible patients, pemetrexed maintenance (non-squamous only following pemetrexed/platinum induction).

Figure 2 Study flow chart



^a Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization.

^b Tumor assessments were performed using RECIST 1.1

^c A confirmatory scan is always required following the initial demonstration of PD and preferably at the next scheduled visit (in the absence of clinically significant deterioration). (See Section 5.1 for more information.)

2. STUDY OBJECTIVES

All objectives will be evaluated for all patients, unless otherwise indicated, and where appropriate for patients with PD-L1-positive and/or PD-L1-negative NSCLC. The assessment of PFS and OS in all patients and PFS in patients with PD-L1-positive NSCLC will be considered co-primary objectives.

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS in patients with PD-L1 positive _{25%} NSCLC	PFS using Blinded Independent Central Review (BICR) assessments according to RECIST 1.1
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC terms of OS in patients with PD-L1 positive _{25%} NSCLC	OS
To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of OS in patients with PD-L1 positive _{25%} NSCLC	OS

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
<p>To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS, OS, objective response rate (ORR), duration of response (DoR), proportion of patients alive and progression free at 12 months from randomization (APF12), and time to second progression (PFS2)</p>	<p>OS in PD-L1 positive_{1%} patients and all patients PFS in PD-L1 positive_{1%} patients and all patients using BICR assessments according to RECIST 1.1 ORR, DoR, and APF12 in patients with PD-L1 positive_{25%} NSCLC, and patients with PD-L1 positive_{1%} NSCLC and all patients using BICR assessments according to RECIST 1.1 PFS2 in patients with PD-L1 positive_{25%} NSCLC, and patients with PD-L1 positive_{1%} NSCLC and all patients using local standard clinical practice^a</p>
<p>To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of PFS, ORR, DoR, APF12, and PFS2</p>	<p>PFS in patients with PD-L1 positive_{25%} NSCLC using BICR assessments according to RECIST 1.1 ORR, DoR, and APF12 in patients with PD-L1 positive_{25%} NSCLC using BICR assessments according to RECIST 1.1 PFS2 in patients with PD-L1 positive_{25%} NSCLC using local standard clinical practice^a</p>
<p>To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, OS, and ORR</p>	<p>PFS and ORR in patients with PD-L1 positive_{25%} NSCLC and all patients using BICR assessments according to RECIST 1.1 OS in patients with PD-L1 positive_{25%} and PD-L1 positive_{1%} NSCLC and all patients</p>
<p>To assess disease-related symptoms and health-related quality of life (HRQoL) in patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC using the EORTC 30-item core quality of life questionnaire, Version 3 (QLQ-C30 v3) and the 13-item lung cancer quality of life questionnaire (QLQ-LC13) module</p>	<p>EORTC QLQ-C30 EORTC QLQ-LC13 Changes in World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status will also be assessed.</p>
<p>To assess the pharmacokinetics (PK) of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy</p>	<p>Concentration of MEDI4736 and tremelimumab in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling)</p>
<p>To investigate the immunogenicity of MEDI4736 and tremelimumab</p>	<p>Presence of anti-drug antibodies (ADAs) for MEDI4736 and tremelimumab</p>

^a PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death, based on Investigator tumor assessments.

2.3 Safety objective

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC in the first-line setting for treatment of advanced or metastatic patients with NSCLC	Adverse events (AEs), physical examinations, laboratory findings, and vital signs

2.4 Exploratory objectives

CCI



CCI

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

Each patient must meet all of the inclusion criteria (Section 3.1) and none of the exclusion criteria (Section 3.2) for this study. Under no circumstances will there be exceptions to this rule.

3.1 Inclusion criteria

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

1. Age \geq 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 US, 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. (For patients aged <20 years and enrolling in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.)
3. Histologically or cytologically documented Stage IV NSCLC not amenable to curative surgery or radiation (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology; [IASLC Staging Manual in Thoracic Oncology](#)).
4. Patients must have tumors that lack sensitizing EGFR mutation (eg, exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) and ALK rearrangement. (If a patient has squamous histology or is known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required).

5. No prior chemotherapy or any other systemic therapy for advanced or metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for advanced disease are eligible, provided that progression has occurred >6 months from last therapy.
6. Tumor PD-L1 status, with the CCI [REDACTED] confirmed by a reference laboratory, must be known prior to randomization. As such, all patients must be able to undergo a fresh tumor biopsy during screening or to provide an available tumor sample taken <3 months prior to enrollment. Tumor lesions used for fresh biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. 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 submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC and CCI [REDACTED].
7. WHO/ECOG performance status of 0 or 1 at enrollment.
8. 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 a short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.
9. No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 anti-(PD-L2) antibodies, excluding therapeutic anticancer vaccines.
10. Adequate organ and marrow function as defined below:
 - Hemoglobin ≥ 9.0 g/dL
 - Absolute neutrophil count $\geq 1.5 \times 10^9$ /L
 - Platelet count $\geq 100 \times 10^9$ /L
 - Serum bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN; for patients with hepatic metastases, ALT and AST $\leq 5 \times$ ULN
 - Calculated creatinine clearance ≥ 50 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24 hour urine collection

Males:

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

Females:

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

11. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
 - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses >1 year ago, had chemotherapy-induced menopause with >1 year interval since last menses, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

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 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 the follow-up period of an interventional study
3. Mixed small-cell lung cancer and NSCLC histology, sarcomatoid variant
4. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

5. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable.
6. 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.
7. History of allogenic organ transplantation
8. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis with the exception of diverticulosis, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea), systemic lupus erythematosus, Sarcoidosis syndrome, or 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
9. Any condition that, in the opinion of the Investigator, would interfere with the 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, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from MEDI4736 or tremelimumab, or compromise the ability of the patient to give written informed consent
10. Medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy
11. History of another primary malignancy except for
 - Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of study drug and of low potential risk for recurrence
 - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
 - Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)

12. History of leptomeningeal carcinomatosis
13. Brain metastases or spinal cord compression unless the patient is stable (asymptomatic, no evidence of new or emerging brain metastases) and off steroids for at least 14 days prior to start of study treatment. Following radiotherapy and/or surgery, patients with brain metastases must wait 4 weeks following the intervention and must confirm stability with imaging before randomization. Patients with suspected brain metastases at screening should have a CT/MRI of the brain prior to study entry.
14. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms
15. History of active primary immunodeficiency
16. Active infection, including tuberculosis (clinical evaluation), hepatitis B, hepatitis C, or human immunodeficiency virus (HIV, positive HIV 1 or 2 antibodies). Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).
17. Current or prior use of immunosuppressive medication within 14 days before the first dose of MEDI4736 or tremelimumab. The following are exceptions to this criterion:
 - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection).
 - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
 - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
18. Receipt of live, attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.
19. 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 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy.

20. Known allergy or hypersensitivity to IP or any excipient or to other humanized mAbs

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 3.4.

3.3 Patient enrollment and randomization

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

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

1. Obtain signed informed consent before any study specific procedures are performed. (Informed consent of study procedures may be obtained prior to the 28-day screening window in order to permit tumor biopsy sample acquisition which must be analyzed prior to randomization.)
2. Obtain a unique 7-digit enrollment number (E-code), through the Interactive Voice Response System (IVRS)/(Interactive Web Response System) IWRS in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). 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 (Obtaining the tumor biopsy sample should be given the highest priority and, as such, the sample may be obtained and sent for PD-L1 expression status evaluation prior to the 28-day screening window in order to permit analysis prior to randomization.)

The sample should be sent only for the patient with known EGFR and ALK status. **If a patient has squamous histology or is known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required.** If EGFR and ALK status is unknown, then the tumor sample (archive or fresh, primary or metastatic) should be used firstly for (local or central) EGFR and ALK mutation testing in accordance to inclusion criterion 4.

4. Determine patient eligibility (see Sections 3.1 and 3.2)
5. Obtain signed informed consent for genetic research study (optional)

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

1. Define the SoC treatment (based on the most appropriate option for the patient) that the patient would receive if randomized to the SoC group prior to randomization of

the patient. This must be completed for all patients. The information will be recorded in the IVRS/IWRS system.

Note, for all patients with non-squamous tumor histology who would be scheduled to receive pemetrexed if randomized to the SoC group, folic acid and vitamin B12 should commence prior to randomization for up to 7 days, in line with local practice. This is to ensure SoC treatment can begin on Day 1.

2. Obtain a unique randomization number via the IVRS/IWRS. Numbers will start at 001 and will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 3 treatment groups. PD-L1 expression status results must be received from the central laboratory by the IVRS/IWRS prior to randomization.

If the patient is ineligible and not randomized, 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 a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

3.4 Procedures for handling incorrectly enrolled patients

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

When a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on treatment, the Investigator should inform the Study Physician immediately, and the Study Physician and the Investigator should discuss whether to continue or discontinue the patient from treatment. The Study Physician must ensure that all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The actual treatment given to patients will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.

One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group.

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for

randomization. The IVRS/IWRS will provide the kit identification number to be allocated to the patient at the randomization visit.

3.6 Methods for ensuring blinding

Not applicable; this study is not blinded.

3.7 Methods for unblinding

Not applicable; this study is not blinded.

3.8 Restrictions

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

1. Female patients of child-bearing potential
 - Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception ([Table 1](#)) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy. Male partners of a female patient must use a male condom plus spermicide (except in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.
2. Male patients with a female partner of childbearing potential
 - Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide (except in countries where spermicides are not approved) from screening through 180 days after receipt of the final dose of MEDI4736 + tremelimumab combination therapy or 90 days after receipt of the final dose of MEDI4736 monotherapy (see [Table 1](#)). Not engaging in sexual activity is an acceptable practice; however, abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
 - It is strongly recommended for the female partner of a male patient to also use a highly effective method of contraception throughout this period.

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

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

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

Highly effective methods of contraception, defined as 1 that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in [Table 1](#). Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Patients in the SoC group: Follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the SoC group.

Table 1 Highly effective^a methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal methods
<ul style="list-style-type: none"> • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)^b • 	<ul style="list-style-type: none"> • Etonogestrel implants: eg, Implanon or Norplan • Intravaginal device: eg, ethinylestradiol and etonogestrel • Medroxyprogesterone injection: eg, Depo-Provera • Normal and low-dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

^a Highly effective (i.e. failure rate of <1% per year)

^b This is also considered a hormonal method

3. All patients: Patients should not donate blood or blood components while participating in this study and for 90 days following the last dose of IP.
4. Restrictions relating to concomitant medications are described in Section 7.7

3.9 Discontinuation of investigational product

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

- 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 is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 3.10.2).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from study treatment (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent

- Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with IP

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. If possible, they will be seen and assessed by an Investigator. AEs will be followed up (see Section 6). The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

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 follow-up (see Table 4). All patients will be followed for survival until the end of the study. Patients who decline to return to the site for evaluations should be contacted by telephone as an alternative.

Any patient who discontinues study treatment for reasons other than objective disease progression should have tumor assessments performed as scheduled in Table 4 until objective disease progression is documented or death occurs, unless consent is withdrawn.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

3.10 Criteria for withdrawal of the patient from the study

3.10.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients can be rescreened a single time, but they cannot be re-randomized.

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. The patient will return electronic PRO devices, if applicable.

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 to continue 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 evaluations should resume according to the protocol.

3.10.3 Survival status for withdrawn consent and lost to follow up patients

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The SURVIVE module will be updated.)
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The SURVIVE module will be updated.)

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

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

In addition, the study may be stopped based on the findings of the interim safety analysis conducted by the Independent Data Monitoring Committee (IDMC) (see Section 6.8).

Regardless of the reason for termination, all data available for the patients 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, AstraZeneca will ensure that adequate consideration is given to the protection of the patients' interests. If this study is discontinued, all other studies involving MEDI4736 or tremelimumab will remain open to enrollment and screening, if deemed appropriate by AstraZeneca.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and the treatment periods in this study are presented for the MEDI4736 + tremelimumab combination therapy group and MEDI4736 monotherapy group in [Table 2](#) and for the SoC therapy group in [Table 3](#). The procedures for the follow-up period are presented in [Table 4](#).

Table 2 Schedule of assessments for MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy treatment and retreatment periods

	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13 ^a etc	For details see Section
Week	-4 to -1	0	4	8	12	16	20	24	28, 32, 36, 40, 44	48 etc	
Day	-28 to -1	1	29	57	85	113	141	169	197, 225, 253, 281, 309	337 etc	
Window (days)	NA	+3 ^b	±3	±3	±3	±3	±3	±3	±3	±3	
Informed consent											
Informed consent: study procedures	X ^c										4.1, 10.4
CCI	■										3.3
Study procedures											
Physical exam (full)	X										5.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	X	X	X	5.2.2
Vital signs ^d	X	X	X	X	X	X	X	X	X	X	5.2.4
ECG ^e	X	As clinically indicated									5.2.3
Concomitant medications	<----->										7.7
Demography, including baseline characteristics and tobacco use	X										4.1
Eligibility criteria	X										3.1, 3.2
Laboratory assessments^f											
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	Table 5
Hematology	X	X	X	X	X	X	X	X	X	X	Table 6
APTT and INR	X	As clinically indicated									Table 6
TSH, free T ₃ , and free T ₄ ^g	X	X	X	X	X	X	X	X	X	X	5.2.1
Urinalysis	X	As clinically indicated									Table 7
Hepatitis B and C and HIV	X										5.2.1

Table 2 Schedule of assessments for MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy treatment and retreatment periods

	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13 ^a etc	For details see Section
Week	-4 to -1	0	4	8	12	16	20	24	28, 32, 36, 40, 44	48 etc	
Day	-28 to -1	1	29	57	85	113	141	169	197, 225, 253, 281, 309	337 etc	
Window (days)	NA	+3 ^b	±3	±3	±3	±3	±3	±3	±3	±3	
Pregnancy test ^h	X	X	X	X	X	X	X	X	X	X	5.2.1
Pharmacokinetics											
MEDI4736 PK sample (serum)		X ⁱ			X ⁱ			X ⁱ			5.4.1
Tremelimumab PK sample (serum; combination therapy group only)		X ⁱ			X ⁱ						5.4.1
Monitoring											
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X	X	5.3.3
AE/SAE assessment	-----<----->-----										6.3.1
Drug accountability		X	X	X	X	X	X	X	X	X	7.6
Pre-randomization medication											
Folic acid ^l	X	Discontinue as randomized to monotherapy or combination therapy									3.3
IM Vitamin B12 ^j	X	Discontinue as randomized to monotherapy or combination therapy									3.3
IP administration											
<i>Combination therapy group</i>											
MEDI4736 (combination therapy) ^{k1}		X	X	X	X	X	X	X	X	X	7.2.1
Tremelimumab ^{ij}		X	X	X	X						7.2.1
<i>Monotherapy group</i>											
MEDI4736 (monotherapy) ^l		X	X	X	X	X	X	X	X	X	7.2.1
PRO assessments^m											

Table 2 Schedule of assessments for MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy treatment and retreatment periods

	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13 ^a etc	For details see Section
Week	-4 to -1	0	4	8	12	16	20	24	28, 32, 36, 40, 44	48 etc	
Day	-28 to -1	1	29	57	85	113	141	169	197, 225, 253, 281, 309	337 etc	
Window (days)	NA	+3 ^b	±3	±3	±3	±3	±3	±3	±3	±3	
EORTC QLQ-C30, CCI	X	Every 4 weeks for the first 8 weeks relative to the date of randomization, then every 8 weeks thereafter until second progression/death (whichever comes first)									5.3.1.1, 5.3.1.5
EORTC QLQ-LC13, CCI	X	Every 2 weeks for the first 8 weeks relative to the date of randomization, then every 4 weeks thereafter until second progression/death (whichever comes first)									5.3.1.2, 5.3.1.3
CCI			X	X	X			X		X	5.3.1.4
Other laboratory assessments and assays											
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)		X			X			X ^o			5.4.2
sPD-L1 (serum)		X			X			X			5.5.2
Circulating soluble factors (plasma)		X	X		X						5.5.2
Tumor biopsy (newly acquired or archived <3 months old)	X ^c										5.5.1
Archival tumor sample ≥3 months old, if available	X										5.5.1
EGFR and ALK test	X ^p										3.3
CCI		█									█
		█	█								█
		█									█
		█	█								█

Table 2 Schedule of assessments for MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy treatment and retreatment periods

	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13 ^a etc	For details see Section
Week	-4 to -1	0	4	8	12	16	20	24	28, 32, 36, 40, 44	48 etc	
Day	-28 to -1	1	29	57	85	113	141	169	197, 225, 253, 281, 309	337 etc	
Window (days)	NA	+3 ^b	±3	±3	±3	±3	±3	±3	±3	±3	
Tumor evaluation (CT or MRI) (RECIST 1.1) ^{g,f}	X	Every 6 weeks ± 1 week for the first 48 weeks relative to the date of randomization, and then every 8 weeks ± 1 week thereafter									5.1
CCI [REDACTED]	█										5.6
Health economics measurements											
CCI [REDACTED]		To be completed at each hospitalization and unscheduled visit by site staff									8.5.7

- Patients who continue on treatment will be assessed in the same manner
- Every effort should be made to minimize the time between randomization and starting treatment. (ie. on the same day after randomization)
- Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. The collection of tumor biopsies at the time of progression prior to retreatment is mandated; the Investigator must consult with the Study Physician if such sampling is not feasible. CCI [REDACTED]
- Body weight is recorded along with vital signs.
- Any clinically significant abnormalities detected require a confirmatory ECG.
- If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.
- Free T₃ and free T₄ will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
- For women of childbearing potential only. A urine or serum pregnancy test is acceptable.
- Pre-dose same day as infusion and within 1 hour of end of infusion.
- To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed if randomized to SoC group.
- During the combination portion of treatment, tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion. If there are no clinically significant infusion reactions with the first cycle, then for all other cycles, the MEDI4736 can be given immediately after the tremelimumab infusion has finished.
- Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion (within 3 days).
- In instances where the PRO assessments coincide with a clinic visit, the research nurse or study coordinator should verify that the questionnaire was completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.
- CCI [REDACTED]
- MEDI4736 sample only at this time point.

- p. For patients with unknown status of ALK and/or EGFR NSCLC. (If patients have squamous histology or are known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required.)
- q. RECIST 1.1 assessments will be performed on CT/MRI images of the chest and abdomen (including liver and adrenal glands). 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 the date of randomization and, ideally, should be performed as close as possible to and prior to the start of study treatment. The radiological progression confirmatory scans should be performed no less than 4 weeks after the prior assessment of PD and preferably at the next scheduled visit (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 their next scheduled visit.
- r. Patients with confirmed PD can continue to receive MEDI4736 + tremelimumab or MEDI4736 at the discretion of the Investigator
- s. CCI [REDACTED]

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

Note: For “retreatment”, the same assessments should be done as in the first treatment period, with the exception of the PK, ADA, , SNP genotyping, and MDSCs assessments, which do not need to be collected a second time.

ADA Anti-drug antibody; AE Adverse event; ALK Anaplastic lymphoma kinase; APTT activated partial thromboplastin time; C Cycle; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; EORTC QLQ-C30 30-item core Eastern Cooperative Oncology Group Quality of Life Questionnaire; EORTC QLQ-LC13 13-item lung cancer EORTC QLQ; CCI [REDACTED]
HIV Human immunodeficiency virus; IM intramuscular; INR international normalized ratio; IP Investigational product; MDSC Myeloid-derived suppressor cell; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; PBMC Peripheral blood mononuclear cell; PD Progressive disease; CCI [REDACTED]
[REDACTED] PGx Pharmacogenetic research; PK Pharmacokinetic(s); CCI [REDACTED]
[REDACTED] RNA Ribonucleic acid; SAE Serious adverse event; SNP Single nucleotide polymorphism; sPD-L1 Soluble programmed cell death ligand 1; TSH Thyroid-stimulating hormone; T₃ Triiodothyronine; T₄ Thyroxine; WHO World Health Organization.

Table 3 Schedule of assessments for Standard of Care therapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc	For details see Section
Week	-4 to -1	0	3	6	9	12	15	18	21	24	27, 30, 33, 36, 39, 42, 45, 48	51, 54, etc	
Day	-28 to -1	1	22	43	64	85	106	127	148	169	190, 211, 232, 253, 274, 295, 316, 337	358, 379, etc	
Window (days)	NA	+3 ^a	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Informed consent													
Informed consent: study procedures	X ^b												4.1, 10.4
Consent: genetic sample and analysis (optional)	X												3.3
Study procedures													
Physical exam (full)	X												5.2.2
Targeted physical exam (based on symptoms)		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	5.2.4
ECG ^d	X	As clinically indicated										5.2.3	
Concomitant medications	<----->											7.7	
Demography, including baseline characteristics and tobacco use	X												4.1
Eligibility criteria	X												3.1, 3.2
Laboratory assessments													
Clinical chemistry ^{e,f}	X	X	X	X	X	X	X	X	X	X	X	X	Table 5
Hematology ^{e,f}	X	X	X	X	X	X	X	X	X	X	X	X	Table 6
APTT and INR	X	As clinically indicated										Table 6	

Table 3 Schedule of assessments for Standard of Care therapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc	
Week	-4 to -1	0	3	6	9	12	15	18	21	24	27, 30, 33, 36, 39, 42, 45, 48	51, 54, etc	For details see Section
Day	-28 to -1	1	22	43	64	85	106	127	148	169	190, 211, 232, 253, 274, 295, 316, 337	358, 379, etc	
Window (days)	NA	+3 ^a	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
TSH, free T ₃ , and free T ₄ ^e	X					X				X			5.2.1
Urinalysis	X	As clinically indicated										Table 7	
Hepatitis B and C and HIV	X												5.2.1
Pregnancy test ^h	X	As clinically indicated										5.2.1	
Monitoring													
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	5.3.3
AE/SAE assessment	<----->											6.3.1	
Pre-randomization medication													
Folic acid ⁱ	X	Continue in line with local practice										3.3	
IM Vitamin B12 ⁱ	X	Continue in line with local practice										3.3	
SoC administration													
Platinum-based chemotherapy		X	Cycle every 3 weeks									7.2.1	
PRO assessments^j													
EORTC QLQ-C30, CCI	X	Every 4 weeks relative for the first 8 weeks relative to the date of randomization, then every 8 weeks thereafter until second progression/death (whichever comes first)										5.3.1.1, 5.3.1.5	
EORTC QLQ-LC13, CCI	X	Every 2 weeks for the first 8 weeks relative to the date of randomization, then every 4 weeks thereafter until second progression/death (whichever comes first)										5.3.1.2, 5.3.1.3	
CCI		Weeks 4, 8, 12, 24, and 48										5.3.1.4	

Table 3 Schedule of assessments for Standard of Care therapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc	For details see Section
Week	-4 to -1	0	3	6	9	12	15	18	21	24	27, 30, 33, 36, 39, 42, 45, 48	51, 54, etc	
Day	-28 to -1	1	22	43	64	85	106	127	148	169	190, 211, 232, 253, 274, 295, 316, 337	358, 379, etc	
Window (days)	NA	+3 ^a	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Other laboratory assessments and assays													
sPD-L1 (serum)		X				X				X			5.5.2
Circulating soluble factors		X		X		X							5.5.2
Tumor biopsy (newly acquired or archived <3 months old)	X ^b												5.5.1
Archival tumor sample ≥3 months old, if available	X												5.5.1
EGFR and ALK test	X ^l												3.3
CCI ██████████		█											█
██████████		█		█									█
██████████		█											█
██████		█		█									█
Tumor evaluation (CT or MRI) (RECIST 1.1) ^m	X	Every 6 weeks ± 1 week for the first 48 weeks relative to the date of randomization, and then every 8 weeks ± 1 week thereafter										5.1	
CCI ██████████	█												5.6

Table 3 Schedule of assessments for Standard of Care therapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc	
Week	-4 to -1	0	3	6	9	12	15	18	21	24	27, 30, 33, 36, 39, 42, 45, 48	51, 54, etc	For details see Section
Day	-28 to -1	1	22	43	64	85	106	127	148	169	190, 211, 232, 253, 274, 295, 316, 337	358, 379, etc	
Window (days)	NA	+3 ^a	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Health economics measurements													
CCI		To be completed at each hospitalization and unscheduled visit by site staff											8.5.7

- a. Every effort should be made to minimize the time between randomization and starting treatment. (ie, on the same day after randomization)
- b. Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization
- c. Before every infusion or administration and as clinically indicated.
- d. Any clinically significant abnormalities detected require a confirmatory ECG.
- e. To be collected every 3 weeks prior to the start of infusion and as clinically indicated.
- f. If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.
- g. Free T3 and free T4 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. To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed if randomized to SoC group.
- j. In instances where the PRO assessments coincide with a clinic visit, the research nurse or study coordinator should verify that the questionnaire was completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures and before discussion of disease progression to avoid biasing the patient’s responses to the questions.
- k. **CCI**
- l. For patients with unknown status of ALK and/or EGFR NSCLC. (If patients have squamous histology or is known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required.)
- m. RECIST 1.1 assessments will be performed on CT/MRI images of the chest and abdomen (including liver and adrenal glands). 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 the date of randomization and, ideally, should be performed as close as possible to and prior to the start of study treatment. The radiological progression confirmatory scans should be performed no less than 4 weeks after the prior assessment of PD and preferably at the next scheduled visit (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 their next scheduled visit.

CCI

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Note: All assessments on treatment days are to be performed prior to infusion or administration, unless otherwise indicated.

ADA Anti-drug antibody; AE Adverse event; ALK Anaplastic lymphoma kinase; APTT activated partial thromboplastin time; C Cycle; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; EORTC QLQ-C30 30-item core Eastern Cooperative Oncology Group Quality of Life Questionnaire; EORTC QLQ-LC13 13-item lung cancer EORTC QLQ; CCI
HIV Human immunodeficiency virus; IM intramuscular; INR international normalized ratio; IP Investigational product; MDSC Myeloid-derived suppressor cell; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; PBMC Peripheral blood mononuclear cell; PD Progressive disease; CCI
PGx Pharmacogenetic research; PK Pharmacokinetic(s); CCI
RNA Ribonucleic acid; SAE Serious adverse event; SNP Single nucleotide polymorphism; sPD-L1 Soluble programmed cell death ligand 1; TSH Thyroid-stimulating hormone; T₃ Triiodothyronine; T₄ Thyroxine; WHO World Health Organization.

Table 4 Schedule of assessments for patients who have completed/discontinued treatment with MEDI4736 + tremelimumab, MEDI4736 monotherapy, or Standard of Care therapy

Evaluation	Time since last dose of IP							
	Day (± 3)	Months (± 1 week)						12 months and every 2 months (± 2 weeks)
	30	2	3	4	6	8	10	
Physical examination (full) ^a	X							
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X							
Weight	X							
Pregnancy test ^b	X	As clinically indicated						
AE/SAE assessment ^c	X	X	X					
Concomitant medications	X	X	X					
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy ^d							
Subsequent anticancer therapy ^e ; and second progression assessment ^{f,g}	<----->							
Survival status ^h		X	X	X	X	X	X	X
Hematology	X	X	X					
Clinical chemistry	X	X	X					
TSH, free T ₃ , and free T ₄ ⁱ	X							
Pharmacokinetic assessment ^l			X					
Immunogenicity assessment (ADA sampling) to identify ADA responses in patient circulation ^l			X		X			
sPD-L1 concentration (to assess target engagement) ^j			X					
EORTC QLQ-C30 ^k , CCI	Every 4 weeks relative for the first 8 weeks relative to the date of randomization, then every 8 weeks thereafter until second progression/death (whichever comes first)							

Table 4 Schedule of assessments for patients who have completed/discontinued treatment with MEDI4736 + tremelimumab, MEDI4736 monotherapy, or Standard of Care therapy

Evaluation	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)
	30	2	3	4	6	8	10	
EORTC QLQ-LC13 ^k CCI	Every 2 weeks for the first 8 weeks relative to the date of randomization, then every 4 weeks thereafter until second progression/death (whichever comes first)							
CCI	X							
Tumor assessment (CT or MRI) ^m	Every 6 weeks ± 1 week for the first 48 weeks (relative to the date of randomization), and then every 8 weeks ± 1 week thereafter until confirmed objective disease progression/death (whichever comes first). Additional scans to be completed per standard practice post progression.							

- a. Physical exams are described in Section 5.2.2.
- b. For women of childbearing potential only. A urine or serum pregnancy test is acceptable.
- c. The AE/SAE follow-up for SoC is only 30 days
- d. WHO/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, WHO performance status should be provided when information on subsequent anticancer therapy is provided, where possible.
- e. Details of any treatment for NSCLC (including surgery) post the last dose of study treatment must be recorded in the eCRF.
- f. PFS2 assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death.
- g. For patients who discontinue their assigned IP following confirmed progression, available readings of CT/MRI from local practice will be collected from the patients' medical charts while information on subsequent anticancer treatment and/or PFS2 is collected.
- h. Patients may be contacted in the week following data cut-offs to confirm survival status. Details of any treatment for NSCLC (including surgery) post the last dose of study treatment must be recorded in the eCRF.
- i. Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
- j. For patients in the MEDI4736 + tremelimumab or MEDI4736 monotherapy groups only. The 3 month follow-up collections for MEDI4736 and Tremelimumab PK and ADA are relative to respective last dose and the 6-month follow-up collections for MEDI4736 and Trememlimumab ADA are relative to respective last dose.
- k. Patients will complete PROs using handheld devices at home.
- l. CCI
- m. Only for patients yet to progress, RECIST 1.1 assessments will be performed on CT/MRI images of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients. The radiological progression confirmatory scans should preferably be performed no less than 4 weeks after the prior assessment of PD and preferably at the next scheduled visit (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 their scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

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ADA Anti-drug antibody; AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; eCRF electronic case report form; EORTC QLQ-C30 Eastern Cooperative Oncology Group Quality of Life Questionnaire; EORTC QLQ-LC13 EORTC QLQ Lung Cancer 13; CCI [REDACTED]
[REDACTED] IP Investigational product; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; PD Progressive disease; PFS2 Time to second progression; CCI [REDACTED] RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; sPD-L1 Soluble programmed cell death ligand 1; TSH Thyroid-stimulating hormone; T₃ Triiodothyronine; T₄ Thyroxine; WHO World Health Organization.

4.1 Enrollment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in [Table 2](#) and [Table 3](#). 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.

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

Screening evaluations may be performed over more than 1 visit.

The timing of vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in [Table 2](#) and [Table 3](#).

4.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule (see [Table 2](#) and [Table 3](#)).

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in [Table 2](#) and [Table 3](#).

4.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule (see [Table 4](#)).

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 timepoints indicated in [Table 4](#).

5. STUDY ASSESSMENTS

A 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 this study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and 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 PFS, ORR, DoR, and APF12 using BICR assessments (primary), and using Investigator assessments for sensitivity analysis. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions and the objective tumor response criteria (CR, PR, SD, or PD) are presented in CCI PFS2 defined by local standard clinical practice, and OS will also be evaluated.

The methods of assessment of tumor burden used at baseline are CT and MRI scans of the chest and abdomen (including liver and adrenal glands). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The baseline assessment should be performed no more than 28 days before randomization and ideally as close as possible to the start of the assigned IP. Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks for the first 48 weeks (relative to the date of randomization; [Table 2](#), [Table 3](#) and [Table 4](#)) then every 8 weeks (q8w) thereafter, until confirmed objective disease progression per 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 their scheduled visits.

For patients who discontinue IP (including SoC) due to toxicity in the absence of confirmed objective progression, objective tumor assessments per the scheduled assessments should be continued every 6 weeks for 48 weeks (relative to randomization) and then every 8 weeks until confirmed objective disease progression.

A confirmatory scan is required for all patients following the initial demonstration of PD. The confirmatory scan should occur no earlier than 4 weeks after the initial assessment of PD and preferably at the next scheduled visit in the absence of clinically significant deterioration. Treatment with MEDI4736 + tremelimumab, MEDI4736 monotherapy, or SoC may continue between the initial assessment of progression and confirmation of progression. Progression would be considered confirmed per RECIST 1.1 criteria available in CCI using Investigator assessments.

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.

Following confirmed progression, patients should continue to be followed up for survival every 1 to 2 months as outlined in the study plan (Table 4). Subsequent anticancer therapy information will be collected at the timepoints indicated in Table 4.

Patients in the MEDI4736 + tremelimumab who will receive retreatment must have a baseline tumor assessment within 28 days of restarting treatment and additional scans every 6 weeks for the first 48 weeks relative to the date of randomization, and then q8w thereafter until disease progression. All assessments in Table 2 will be followed for patients who receive retreatment.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans (Table 2 and Table 3 [screening and the treatment period] and Table 4 for follow-up of patients who have completed or discontinued IP treatment]) and CCI

5.1.1 Central reading of scans

A BICR of all radiological scans in accordance with RECIST 1.1 will be performed for the evaluation of the co-primary PFS endpoint (and all secondary endpoints determined from the tumor assessments).

All images will be collected centrally. Guidelines for imaging collection and storage will be provided in a separate document. Results of these independent reviews will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST1.1 assessment conducted by the Investigator.

5.1.2 Survival assessments

Assessments for survival must be made every 2 months following treatment discontinuation. Survival information may be obtained via telephone contact with the patient, patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the data cut-off for the primary analysis of PFS and for each interim and final analysis of OS to provide complete survival data. These contacts should generally occur within 7 days of the data cut off.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood samples for determination of clinical chemistry and hematology will be taken at the times indicated in the assessment schedules and as clinically indicated (see [Table 2](#), [Table 3](#) and [Table 4](#)). Urine samples for analysis will be taken at screening.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed 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 (urine or serum pregnancy test). 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, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in [Table 5](#) (clinical chemistry), [Table 6](#) (hematology), and [Table 7](#) (urinalysis).

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum β -hCG) samples will be performed for pre-menopausal women of childbearing potential at screening and subsequent visits as specified in the assessment schedule (see [Table 2](#), [Table 3](#) and [Table 4](#)). Tests will be performed by the hospital's local laboratory. If results are positive, the patient must not start or continue 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 HBV surface antigen, HCV antibodies, HIV antibodies, thyroid-stimulating hormone, free triiodothyronine (T_3), and free thyroxine (T_4).

Table 5 Clinical chemistry (serum or plasma)

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

^a In the event that amylase and lipase analyses cannot be performed, 1 or the other will be performed in line with local practice.

^b If total bilirubin is $\geq 2 \times$ ULN (and evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

^c At screening and as clinically indicated.

Table 6 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	Activated partial thromboplastin time and international normalized ratio ^a

^a Activated partial thromboplastin time and international normalized ratio are to be assessed at screening and as clinically indicated.

Table 7 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

If a patient shows an AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN, refer to **CCI** 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 $\geq 1.5 \times \text{ULN}$) 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 97

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, unless these values are not likely to improve because of the underlying disease.

5.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (see [Table 2](#), [Table 3](#) and [Table 4](#)). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section [6.1.4](#).

5.2.3 Electrocardiograms

Resting 12-lead electrocardiograms (ECGs) will be recorded at screening and as clinically indicated throughout the study (see [Table 2](#) and [Table 3](#)). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

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

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

Situations in which ECG results should be reported as AEs are described in Section [6.1.4](#).

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](#), [Table 3](#) and [Table 4](#)). Body weight is also recorded along with vital signs.

Supine or semi-supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will

be collected from patients in the MEDI4736 + tremelimumab and MEDI4736 monotherapy treatment groups at the following times (based on a 60-minute infusion):

For the first infusion, patients in the MEDI4736 + tremelimumab and MEDI4736 monotherapy treatment groups will be monitored as follows:

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes)
- 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 at the Investigator's discretion (suggested 30 minutes after each MEDI4736 and tremelimumab infusion).

On subsequent infusion days, patients in the MEDI4736 + tremelimumab and MEDI4736 monotherapy treatment groups will be monitored at the start of the infusion and then per institution standard and as clinically indicated.

Patients in the SoC group will be monitored before every infusion or administration and as clinically indicated.

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 6.1.4.

5.3 Other assessments

5.3.1 Patient-reported outcomes

“PRO” is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered in this study: EORTC QLQ-C30 (core questionnaire), QLQ-LC13 (lung cancer module), CCI

The PRO instruments will be completed by the patients using a handheld ePRO device. All assessments should be completed without assistance from anyone according to the assessment

schedules (see [Table 2](#), [Table 3](#) and [Table 4](#)). It takes approximately 30 to 45 minutes for patients to complete the questionnaires; therefore, the burden to the patient is moderate.

5.3.1.1 EORTC QLQ-C30

The EORTC QLQ-C30 v3 questionnaire is included for the purpose of assessing HRQoL and is a well-established measure of HRQoL/health status, and commonly used as an endpoint in cancer clinical trials. It assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. Six single-item symptom measures are also included: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (see [CCI \[REDACTED\]](#)). For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms ([Aaronson et al 1993](#)).

5.3.1.2 EORTC QLQ-LC13

For patients with NSCLC, a disease-specific 13-item self-administered questionnaire for lung cancer was developed (QLQ-LC13; [CCI \[REDACTED\]](#)) to be used in conjunction with the EORTC QLQ-C30 ([Bergman et al 1994](#)). It comprises both multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, hemoptysis, dyspnea, and pain) and side effects from conventional chemotherapy and radiotherapy (ie, hair loss, neuropathy, sore mouth, and dysphagia). Similar to the EORTC QLQ-C30, all questions except 1 have a 4-point scale: “Not at all,” “A little,” “Quite a bit,” and “Very much.” One question (#43 “Did you take any medicine for pain?”) has a response option of “Yes” or “No.” The scoring approach for the QLQ-LC13 is similar to the EORTC QLQ-C30.

[CCI \[REDACTED\]](#)



CCI

CCI

5.3.2 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using a handheld electronic device (ePRO).

Each center must allocate the responsibility for the administration of the PRO devices to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be completed per the schedule of assessments (see [Table 2](#), [Table 3](#) and [Table 4](#)). Patients will be instructed to bring their handheld devices to every clinic visit. In instances where the PRO assessments coincide with a clinic visit, the research nurse or study coordinator should verify that the questionnaire was completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- The research nurse or appointed site staff must explain the value and relevance of participation to patients and inform them that these questions are being asked in order to find out from them directly how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patient has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor, and also provide guidance on whom to call if there are problems with the device.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items. The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.
- The research nurse or appointed site staff must monitor compliance; minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 85%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

5.3.3 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see [Table 2](#), [Table 3](#) and [Table 4](#)) based on the following:

3. Fully active; able to carry out all usual activities without restrictions
4. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)
5. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.
6. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
7. Completely disabled; unable to carry out any self-care and totally confined to bed or chair

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

5.4 Pharmacokinetics

5.4.1 Collection of samples and determination of drug concentration

Blood samples for determination of MEDI4736 and tremelimumab concentration in serum will be obtained according to the assessment schedules (see [Table 2](#) and [Table 4](#)).

CCI



5.4.2 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to the assessment schedules (see [Table 2](#), and [Table 4](#)).

CCI



5.4.3 Storage and destruction of pharmacokinetic/ADA samples

PK and ADA samples will be disposed of a maximum of 10 years after the IPs are approved for marketing.

PK and ADA samples may be disposed of or destroyed and 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.

CCI

CCI



5.5 Biomarker analysis

CCI



CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.5.1 Collection of patient samples for stratification by PD-L1

At screening, there are 2 mandatory options for provisions of tissue to be used for determination of eligibility. There is 1 subsequent mandatory provision of tissue at progression if retreatment is planned:

- **MANDATORY:** Provision of a recent tumor biopsy formalin fixed and embedded in paraffin. A freshly collected tumor biopsy is strongly preferred; however, if not clinically feasible, an archival sample taken less than 3 months prior to screening may be submitted.

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 this 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 to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC analyses (see the Laboratory Manual). Newly acquired or archived specimens with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status.

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 (preferably core needle biopsy), the lesion must be imaged after biopsy prior to randomization.

- **MANDATORY:** The collection of additional archived tumor tissue block greater than 3 months old (formalin-fixed paraffin-embedded) is mandated, where such samples exist in a quantity sufficient to allow for analysis. 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.
- **MANDATORY:** The collection of tumor biopsies at the time of progression prior to retreatment is mandated. The Investigator can consult with the Study Physician if such sampling is not feasible, but retreatment is indicated.
- **OPTIONAL:** The collection of additional biopsies upon progression of patients in the MEDI4736 + tremelimumab and MEDI4736 monotherapy groups is strongly encouraged.
- Additional tumor biopsies collected as part of clinical care (eg, for mixed responses or upon PD) can be submitted for further analysis.

See the Laboratory Manual for further details of requirements including sample QC and shipping.

CCI

The CCI will be used to determine PD-L1 IHC status in this study for the purposes of stratification and for the analysis of the original diagnostic sample.

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

5.5.2 Exploratory biomarkers

CCI

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

Myeloid-derived suppressor cells

CCI [Redacted]

CCI
[Redacted text block]

Peripheral blood mononuclear cells

CCI
[Redacted text block]

Soluble factors - plasma

CCI
[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

CCI

Tumor markers

CCI

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 end of study, after which they will be destroyed. CCI

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 CCI "IATA 6.2 Guidance Document."

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.

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-designated Biobank 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 documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

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

Refer to CCI for details of the genetic research (optional DNA component).

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 during or following exposure to a pharmaceutical product, whether or not the condition is considered to be causally related to the product. An undesirable medical condition can be a symptom (eg, nausea or chest pain), sign (eg, tachycardia or enlarged liver), or the abnormal result 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.

6.1.1 Causality collection

The Investigator will assess the causal relationship between the IPs 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 medications 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 CCI

6.1.2 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 MEDI4736 +/- tremelimumab and 30 days after last dose of SoC) 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.

6.1.3 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.

6.1.4 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements 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 IPs.

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. Whenever possible, the reporting Investigator should use 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 AEs.

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.

6.1.5 Hy’s law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Further instruction on cases of increases in liver biochemistry and evaluation of Hy’s law. Further instruction on cases of increases in liver biochemistry and evaluation of Hy’s law are shown in CCI

6.1.6 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.

6.1.7 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.

6.1.8 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.

6.1.9 Safety Data to be Collected Following the Final DCO of the Study

For patients continuing to receive durvalumab treatment 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 with durvalumab in order to manage AEs in accordance with the durvalumab toxicity management guidelines (CCI). 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 that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 6.4.

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 or 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 **CCI**

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 of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of MEDI4736+/- tremelimumab and 30 days after last dose of SoC). AEs and SAEs collected prior to randomization will be reported as pre-randomization AEs and SAEs. If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

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 for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued on study drug or the study has completed.

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 collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- 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 it is not an 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 it would be an SAE if it satisfies the criteria shown in Section 6.2.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not they are considered causally related to the IPs or to any study procedure. All SAEs will be recorded in the eCRF.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all 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 in which important or relevant information is missing, active follow-up is undertaken immediately. The Investigator or other site personnel will 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 Investigator or other site personnel indicates that an AE is serious in the WBDC system, an automated e-mail alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel will report an 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 MEDI4736 and tremelimumab.

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 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 in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

If an overdose of an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel will inform appropriate AstraZeneca representatives immediately, or **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.

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

6.6 Pregnancy

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

6.6.1 Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy. Please follow the local prescribing information relating to contraception and the time limit for such precautions for SoC agents.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (EC)/Internal Review Boards (IRB) prior to use.

6.7 Management of investigational product-related toxicities

For guidance on the management of IP-related toxicities, please see CCI [REDACTED]

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 (see Section 6.7.2). In addition, guidelines on dose modifications are provided in CCI [REDACTED]
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, guidelines on dose modification and toxicity management for immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 and tremelimumab will be provided to investigators CCI [REDACTED]. 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.

There are certain circumstances in which MEDI4736 and tremelimumab should be permanently discontinued. Following the first dose of IP, subsequent administration of MEDI4736 and tremelimumab can be modified. All toxicities will be graded according to CTCAE Version 4.03. Dose reductions are not permitted. Dose modifications of MEDI4736 and tremelimumab may be required in the event of treatment-related toxicity. All toxicities will be graded according to NCI CTCAE Version 4.03. In case of doubt, the Investigator should consult with the Study Physician.

Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered prior to infusion at the discretion of the Investigator for primary prophylaxis against infusion-related reactions. In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of IP may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (eg, diphenhydramine) and/or corticosteroid or equivalent medications per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If the infusion-related reaction is Grade 3 or higher in severity, treatment with IP will be discontinued.

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

6.7.1 MEDI4736 + tremelimumab and MEDI4736 monotherapy 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 MEDI4736 \pm tremelimumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and that 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 MEDI4736 monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AE 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 AE being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with MEDI4736 ± tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (ie, 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 (eg, presenting symptoms) can be found in the current version of the MEDI4736 IB. More specific guidelines for their evaluation and treatment are described in detail in CCI

6.7.2 Immune-mediated adverse events

Based on the mechanism of action of MEDI4736 and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing imAEs during the conduct of this study. Potential imAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Brahmer et al 2012, Hodi et al 2010, Topalian et al 2012). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include imAEs could potentially occur at higher frequencies than with either MEDI4736 or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of colitis, dermatitis, pneumonitis, hepatitis, and

endocrinopathy. Dose modification guidelines are provided in (CC) and it is recommended that:

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

6.7.3 Standard of Care agents

IP-related toxicity management, including dose delays, reductions, and adjustments for patients in the SoC group should be performed as indicated in the local prescribing information for the relevant agent.

6.8 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.

An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 30 patients have been randomized, whichever occurs first, to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter.

Full details of the IDMC procedures, processes, and interim analyses can be found in the statistical analysis plan and the IDMC Charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca will supply MEDI4736 and tremelimumab, while the SoC treatments (paclitaxel + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, pemetrexed + cisplatin, pemetrexed + carboplatin, and pemetrexed maintenance) will be supplied locally ([Table 8](#)).

Table 8 List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
MEDI4736	50 mg/mL, solution, IV	MedImmune
Tremelimumab	20 mg/mL, solution, IV	MedImmune
Standards of Care		
Paclitaxel ^a	IV (as sourced locally)	Sourced locally
Carboplatin ^a	IV (as sourced locally)	Sourced locally
Gemcitabine ^a	IV (as sourced locally)	Sourced locally
Cisplatin ^a	IV (as sourced locally)	Sourced locally
Pemetrexed ^a	IV (as sourced locally)	Sourced locally

^a Under certain circumstances when local sourcing is not feasible, a Standard of Care treatment may be supplied centrally through AstraZeneca.

IV, intravenous.

7.1.1 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. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Preparation of MEDI4736 doses 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 20 mg/kg will be administered using an IV bag containing 0.9% weight/volume (w/v) saline or 5% (w/v) dextrose, with a final MEDI4736 concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter.

Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. A volume of 0.9% (w/v) saline or 5% (w/v) dextrose equal to the calculated volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to addition of MEDI4736. The calculated volume of MEDI4736

is then added to the IV bag such that final concentration is within 1 mg/mL to 20 mg/mL. The bag is mixed by gentle inversion 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. In the event that either preparation time or infusion time exceeds the time limit, a new dose must be prepared using new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between MEDI4736 and polyvinylchloride or polyolefin have been observed.

Dose calculation

The volume of MEDI4736 (in mL) to add to the IV bag is calculated as follows:

$$20 \text{ mg/kg} \times \text{patient weight (kg)} \div \text{MEDI4736 concentration (nominal: 50 mg/mL)}$$

Example: For a patient weighing 80 kg, dosed at 20 mg/kg, 32 mL [20 mg/kg \times 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted into an IV bag such that the final MEDI4736 concentration is within 1 to 20 mg/mL (100 – 1000 mL bag sizes). First, 32 mL of IV bag diluent is removed from the IV bag, and then 32 mL of MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described above.

7.1.2 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 dihydrate and 0.02% (w/v) polysorbate 80; it has a pH of 5.5. The nominal fill volume is 20 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

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 start of administration should not exceed

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

A dose of 1 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.15 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 μm or 0.22 μm in-line filter.

Patient weight at baseline should be used for dosing calculations unless there is a $\geq 10\%$ change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. The volume of 0.9% (w/v) 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 is then added to the IV bag such that final concentration is within 0.15 mg/mL to 10 mg/mL. The bag is then mixed 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. In the event that either preparation time or infusion time exceeds the time limit, a new dose must be prepared using new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. However, polycarbonate syringes and administration set containing cellulose-based filters should not be used with tremelimumab.

Dose calculation of tremelimumab

The volume of tremelimumab (in mL) to add to the IV bag is calculated as follows:

In combination with MEDI4736: $1 \text{ mg/kg} \times \text{patient weight (kg)} \div \text{tremelimumab concentration (nominal: 20 mg/mL)}$

Example: For a patient weighing 80 kg, dosed at 1 mg/kg, 4 mL [$1 \text{ mg/kg} \times 80 \text{ kg}$ divided by 20 mg/mL] of tremelimumab is to be diluted into 0.9% (w/v) saline bag such that the final tremelimumab concentration is within 0.15 to 10 mg/mL (100 – 500 mL bag sizes). First, 4 mL of IV bag diluent is removed from the IV bag, and then 4 mL of tremelimumab is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted tremelimumab is administered as described above..

7.1.3 Standard of Care treatment

Each SoC agent will be sourced as commercially available material/locally sourced, prescribed according to local regulations, and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, an SoC will be supplied centrally by AstraZeneca. This will be labeled with local language translated text in accordance with regulatory guidelines.

7.2 Dose and treatment regimens

Patients will be randomized in a 1:1:1 ratio to receive treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC.

7.2.1 Treatment regimens

MEDI4736 + tremelimumab combination therapy

Patients in the MEDI4736 + tremelimumab combination therapy group will receive 20 mg/kg MEDI4736 via IV infusion q4w for up to 4 doses/cycles and 1 mg/kg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 20 mg/kg MEDI4736 q4w starting on Week 16 (see Figure 3). Dosing outside the window should be discussed with the Study Physician. 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 an 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 at the Investigator’s discretion (suggested 30 minutes after each MEDI4736 and tremelimumab infusion).

Figure 3 MEDI4736 + tremelimumab combination therapy dosing scheme

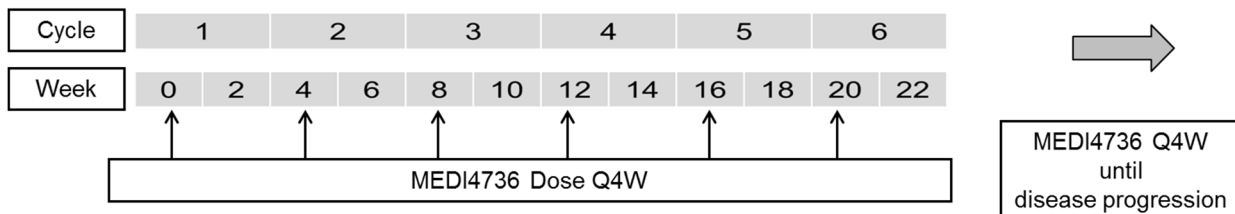


Q4W every 4 weeks.

MEDI4736 monotherapy

Patients in the MEDI4736 monotherapy treatment group will receive 20 mg/kg MEDI4736 via IV infusion q4w (see Figure 4).

Figure 4 MEDI4736 monotherapy dosing scheme



Q4W every 4 weeks.

Standard of Care treatment

Patients in the SoC group will receive 1 of the following treatments until documented PD (unconfirmed and confirmed), initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent to continued treatment, or other reasons to discontinue treatment criterion occur:

- Paclitaxel + carboplatin: Paclitaxel 200 mg/m² and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m² via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m² via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m² via IV infusion on Days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Pemetrexed + cisplatin (non-squamous patients only): Pemetrexed 500 mg/m² and cisplatin 75 mg/m² via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy.
- Pemetrexed + carboplatin (non-squamous patients only): Pemetrexed 500 mg/m² and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy.

For all SoC therapies, a particular treatment (paclitaxel, gemcitabine, cisplatin, carboplatin, or pemetrexed) will not be used in patients who have experienced recurrence or progression of disease within 6 months of prior multimodal therapy using that particular treatment.

A confirmatory scan is required for all patients in the SoC group, even if a subsequent treatment is started.

7.2.2 Duration of treatment and criteria for retreatment

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients in all groups will continue therapy until disease progression.

Progression during treatment

At the Investigator's discretion, patients in all groups may continue receiving therapy in the setting of unconfirmed PD until PD is confirmed. According to RECIST 1.1 modified for confirmation of progression, a confirmatory scan is required following an overall time-point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

Patients in all groups, excluding the SoC arm, with PD according to RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment for as long as they are gaining clinical benefit.

However, patients in the immunotherapy group(s) will not be permitted to continue immunotherapy if progression occurs in a target lesion that has previously shown a confirmed response. Confirmed response is CR or PR, as defined by RECIST 1.1.

Patients in the MEDI4736 + tremelimumab group may restart treatment with the combination therapy if they complete the 4 dosing cycles with MEDI4736 + tremelimumab (with clinical benefit per Investigator's judgment), but subsequently have PD during treatment with MEDI4736 alone and if they meet eligibility criteria for retreatment.

For all groups, excluding the SoC arm, treatment through progression and retreatment in the MEDI4736 + tremelimumab combination therapy group 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 provide further benefit. 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 for retreatment in the setting of PD. This consent document will specify that treatment beyond initial evidence of PD is not the SoC

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 WHO 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

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive durvalumab treatment 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 durvalumab in order to manage AEs in accordance with the durvalumab toxicity management guidelines (please see Section 6.1.9).

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 durvalumab 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 visits assessment per its protocol. Any patient that would be proposed to move to such study would be given a new Informed Consent.

7.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. 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. The IP label on the pack/bottle/carton specifies the appropriate storage. Storage is also described in the IB.

7.5 Compliance

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

Treatment compliance will be assured by reconciliation of site drug accountability logs.

7.6 Accountability

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

Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site, 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 the end of the clinical treatment phase of the study including the 3 month follow up period following the last dose of study drug. Any concomitant medication(s), including herbal preparations, taken during this time will be recorded in the eCRF.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines in **CCI** For agents in the SoC arm, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Prohibited medication/class of drug:	Usage:
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment (including SoC)
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment (including SoC) through 90 days after the last dose of IP.
Any concurrent chemotherapy, local therapy (except palliative radiotherapy for non-target lesions, eg, radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment (including SoC). (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.)

Prohibited medication/class of drug:	Usage:
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor - α blockers	Should not be given whilst the patient is on IP treatment (including SoC). (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Systemic corticosteroids may be used for prevention of chemotherapy-related toxicities (nausea/vomiting prevention and prophylaxis) A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of the patient (eg, for chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties	Should be used with caution for 90 days after the last dose of tremelimumab during the study
Herbal or natural remedies (all herbal or natural remedies, rather than those for constipation only)	Should be avoided for 90 days after the last dose of MEDI4736 monotherapy or combination treatment (MEDI4736+ tremelimumab)
Sunitinib	Should not be given within 3 months of a dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC) during the study
EGFR TKIs	Should not be given concomitantly whilst the patient is on study treatment. In addition they should be used with caution in the 90 days after the last dose of durvalumab. (Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1 st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly).

Rescue/supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as “prohibited” as listed above	To be administered as prescribed by the Investigator

Rescue/supportive medication/class of drug:	Usage:
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc])	Should be used when necessary for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

7.7.1 Other concomitant treatment

Medications 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 should be 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 receiving MEDI4736 + tremelimumab or MEDI4736 monotherapy (see Section 7.2.2).

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of the first randomized patient and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data. The primary aim of the study is to compare the efficacy and safety of MEDI4736 in combination with tremelimumab and MEDI4736 monotherapy to SoC.

8.2 Sample size estimate

The study will plan to enroll approximately 1850 patients in order to randomize 1092 eligible patients 1:1:1 to MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC. The 1092 patients will comprise approximately 480 patients who have PD-L1 positive_{25%} tumors.

The study is sized to characterize the OS benefit of MEDI4736 in combination with tremelimumab and MEDI4736 monotherapy versus SoC in patients with EGFR and ALK wild-type advanced or metastatic NSCLC in patients with PD-L1 positive_{25%} tumors and PFS benefit of MEDI4736 in combination with tremelimumab versus SoC in patients with PD-L1 positive_{25%} tumors. CCI

Two interim analysis of OS will be performed; the first at the time of the primary PFS analysis and the second when 80% of the target OS events have occurred. The alpha will be split between the 3 OS analyses using the Lan and DeMets ([Lan and DeMets 1983](#)) spending function that approximates an O'Brien Fleming approach, with the boundaries for the treatment comparison derived based upon the exact number of OS events at the time of analysis.

The primary PFS analysis for superiority will be performed when both of the following conditions have been met:

- Approximately 231 BICR PFS events have occurred across the MEDI4736 + tremelimumab and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (72% maturity) AND
- CCI to the study

The final (primary) OS analysis for superiority will be performed when the following conditions have been met:

- Approximately 225 OS events have occurred across the MEDI4736 + tremelimumab and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (70% maturity) AND

- Approximately 225 OS events have occurred across the MEDI4736 monotherapy and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (70% maturity)

MEDI4736 + tremelimumab versus SoC (PFS in PD-L1 positive_{25%} population)

CCI

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MEDI4736 + tremelimumab versus SoC (OS in PD-L1 positive_{25%} population)

CCI

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MEDI4736 monotherapy versus SoC (OS in PD-L1 positive_{25%} population)

CCI

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MEDI4736 + tremelimumab versus SoC (OS in PD-L1 positive_{1%} population)

CCI

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CCI



MEDI4736 + tremelimumab versus SoC (OS, all patients)

CCI



MEDI4736 monotherapy versus SoC (PFS in PD-L1 positive_{25%} population)

CCI



MEDI4736 + tremelimumab versus SoC (PFS in PD-L1 positive_{1%} population)

CCI [Redacted]

MEDI4736 + tremelimumab versus SoC (PFS, all patients)

CCI [Redacted]

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 9.

Table 9 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
PFS and OS	PD-L1 positive _{25%} analysis set
PFS and OS	PD-L1 positive _{1%} analysis set
PFS and OS	Full analysis set (ITT population)
ORR, DoR, APF12, PFS2, PROs, and symptom endpoints	PD-L1 positive _{25%} analysis set
ORR, DoR, APF12, PFS2, PROs, and symptom endpoints	PD-L1 positive _{1%} analysis set
PFS, OS, ORR, , DoR, APF12, PFS2	PD-L1-low/negative analysis set
ORR, DoR, APF12, PFS2, PROs, and symptom endpoints	Full analysis set (ITT population)
PK data	PK analysis Set

Outcome variable	Population
Safety Data	
Exposure	Safety analysis Set
AEs	Safety analysis Set
Laboratory measurements	Safety analysis Set
Vital signs	Safety analysis Set
ECGs	Safety analysis Set

8.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients. The full analysis set will be used for all efficacy analyses (including PROs). Treatment groups will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment group to which they were randomized.

8.3.2 PD-L1 positive_{25%} analysis set

The PD-L1 positive_{25%} analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 positive_{25%} as defined by the CCI [REDACTED] (ie, $\geq 25\%$ PD-L1–membrane expression in tumoral tissue).

8.3.3 PD-L1 positive_{1%} analysis set

The PD-L1 positive_{1%} analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 positive_{1%} as defined by the CCI [REDACTED] (ie, $\geq 1\%$ PD-L1–membrane expression in tumoral tissue). This analysis set will be used for for supportive analyses of efficacy endpoints.

8.3.4 PD-L1- low/negative analysis set

The PD-L1-low/negative analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 low/negative as defined by the CCI [REDACTED] (ie, $< 25\%$ PD-L1–membrane expression in tumoral tissue).

8.3.5 PD-L1- negative analysis set

The PD-L1-negative analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 negative as defined by the CCI [REDACTED] (ie, $< 1\%$ PD-L1–membrane expression in tumoral tissue).

8.3.6 Safety analysis set

The safety analysis set (SAS) will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized using the SAS, according to the treatment received, that is, erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

8.3.7 Pharmacokinetic analysis set

All patients who received at least 1 dose of IP per the protocol for whom any post-dose data are available 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. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

The analysis of the co-primary endpoint, PFS, and the analyses of the secondary endpoints, ORR, DoR, and APF12, will be based on BICR tumor assessments according to RECIST 1.1. OS will be evaluated as a co-primary endpoint from all-cause mortality. Additionally, PFS2 will be defined by local clinical practice.

A sensitivity analysis of PFS will be performed using the Investigator tumor assessments 



8.4.2 RECIST 1.1-based endpoints

Blinded Independent Central Review of RECIST 1.1-based assessments

The BICR will be performed on all radiological scans of all patients. All images will be collected centrally. Prior radiotherapy reports will also be provided to the BICR to allow the selection of appropriate target lesions. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or not evaluable [NE]). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (of PFS) will be derived from the scan dates.

Further details of the BICR will be documented in the BICR Charter.

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 randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD).

The definitions of CR, PR, SD, and PD are given in **CCI**

8.4.2.1 Co-Primary endpoints

OS and PFS are the co-primary endpoints.

Progression-free survival

PFS (per RECIST 1.1 using BICR assessments) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized 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 0 days 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:

- The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of either reviewer where both select PD as a time point response and there is no adjudication for central review (BICR).
- For investigational assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component 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.

Note: For target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the target lesions, and similarly for non-target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.



PFS by irRECIST 1.1 criteria using BICR assessments will also be reported.

Overall survival

OS is defined as the time from the date of randomization 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 following the date of data cut-off for the analysis (these contacts should generally occur within 7 days of the data cut off). If patients are confirmed to be alive or if the death date is after 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.

8.4.2.2 Secondary endpoints

Objective response rate

ORR (per RECIST 1.1 using BICR assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

ORR will also be obtained using the algorithm described above for the RECIST 1.1 site Investigator tumor data.

ORR by irRECIST 1.1 criteria using BICR assessments will also be reported.

Duration of response

DoR (per RECIST 1.1 using BICR assessments) 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 time of the initial response will be defined as the latest of the dates contributing towards 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.

Time from randomization to second progression (PFS2)

PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Second progression status will be reviewed (every 6 weeks for the first 48 weeks relative to the date of randomization and then every 8 weeks thereafter) following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, that is, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

Proportion of patients alive and progression free at 12 months

The APF12 will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed using BICR assessments) at 12 months.

Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST 1.1 assessment, described in CCI. It is the best response a patient has had during their time in the study up until RECIST progression or the last evaluable assessment in the absence of RECIST.1.1 progression, as determined by BICR.

Categorization of BoR will be based on RECIST CCI using the following response categories: CR, PR, SD, PD, and NE.

BoR will be determined programmatically based on RECIST 1.1 using all BICR assessments 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 ≤ 90 days (ie, $2 \times (6 \text{ weeks} \pm 3 \text{ days})$) after randomization, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs > 90 days (ie, $2 \times (6 \text{ weeks} \pm 3 \text{ days})$) after the date of randomization then BoR will be assigned to the NE category.

Progression events that have been censored due to them being > 90 days after the last evaluable assessment will not contribute to the BoR derivation.

8.4.3 Calculation or derivation of safety variables

8.4.3.1 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. Any AE occurring within 90 days of discontinuation of the last dose of MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy, or within 30 days of the last dose of SoC) may be included in the AE summaries, but the majority of those summaries will omit those AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy, or more than 30 days after discontinuation of SoC will be produced. These events will not be included in AE summaries.

8.4.3.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

8.4.3.3 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.

The 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 formulas:

$Corrected\ calcium\ (mmol/L) = Total\ calcium\ (mmol/L) + ([40 - albumin\ (G/L)] \times 0.02)$

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.

8.4.4 Calculation or derivation of patient-reported outcome variables

PRO questionnaires, a secondary endpoint of interest will be assessed using the EORTC QLQ-C30 with the QLQ-LC13 module (HRQoL and lung cancer specific symptoms), CCI

[REDACTED] All items/questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available. All PRO analyses will be based on the Full Analysis Set (FAS; ITT population), and the PD-L1 positive_{25%} and PD-L1 positive_{1%} analysis sets, unless otherwise stated. The clinical meaningfulness threshold of the PRO analyses described below will be provided in the SAP.

8.4.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

Changes in score compared with baseline will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Time to HRQoL/function deterioration

For the following HRQoL items of the EORTC QLQ-C30, time to deterioration will be analyzed:

The Global Health Status/ QoL scale consisting of items 29 and 30 of the EORTC QLQ-C30. Item 29: How would you rate your overall health during the past week? Item 30: How would you rate your overall quality of life during the past week? Patients are asked to rate their overall health and overall quality of life on a scale from 1 (very poor) to 7 (excellent).

Time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to HRQoL/function deterioration. Patients with a single deterioration and no further assessments will be treated as deteriorated in the analysis.

Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the HRQoL/function change could be evaluated.

Patients whose HRQoL (as measured by EORTC QLQ-C30) has not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the HRQoL/function could be evaluated. CCI

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement in that symptom from baseline.

HRQoL/function improvement rate

The HRQoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement in that scale from baseline.

8.4.4.2 Lung cancer module (EORTC QLQ-LC13)

The QLQ-LC13 is a lung cancer specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication. Changes in score compared with baseline will be evaluated.

Time to symptom deterioration

For each of the following key symptom scales/items in the QLQ-LC13 and QLQ-C30, time to deterioration will be analyzed:

- Dyspnoea (multi-item scale based on three questions: “Were you short of breath when you rested; walked; climbed stairs”) LC13,
- Cough: one item (“How much did you cough?”), LC13
- Pain: three individual items (“Have you had pain in your chest; your arm or shoulder; other parts of your body?”). LC13
- Appetite Loss (“Have you lacked appetite?”) C30
- Fatigue (“Have you felt weak?”, “Did you need to rest?” “Were you tired?”) C30

The dyspnea scale is only used if all 3 items have been scored; otherwise the items are treated as single-item measures. The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30.

Time to symptom deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful symptom deterioration that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration. Patients with a single deterioration and no further assessments will be treated as deteriorated in the analysis.

Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by QLQ-LC13) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement in that symptom from baseline.

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8.4.5 Calculation or derivation of pharmacokinetic variables

8.4.5.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modeling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. CCI

The results of such an analysis will be reported in a separate report. The PK, pharmacodynamic, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

8.4.5.2 Pharmacokinetic non-compartmental analysis

The PK analyses will be performed at AstraZeneca. The actual sampling times will be used in the PK calculations. PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. PK parameters will be determined using standard non-compartmental methods. CCI

Samples below the lower limit of quantification will be treated as missing in the analyses.

8.4.5.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against MEDI4736 and tremelimumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. CCI

8.4.6 Calculation or derivation of biomarker variables

Biomarker status, as defined in the secondary objectives, will be assessed according to pre-specified criteria that will be detailed in the SAP.

8.5 Methods for statistical analyses

The formal statistical analysis will be performed to test the main hypotheses:

- H0: No difference between MEDI4736 + tremelimumab and SoC
- H1: Difference between MEDI4736 + tremelimumab and SoC

The co-primary endpoints are OS and PFS in patients with PD-L1 positive_{25%} tumors (with PFS using BICR assessments per RECIST 1.1). The study has been sized to characterize the OS and PFS benefits of MEDI4736 + tremelimumab versus SoC in patients with PD-L1 positive_{25%} and OS benefit of MEDI4736 monotherapy versus SoC in patients with PD-L1 positive_{25%} tumors.

The primary PFS analysis for superiority will be performed when both of the following conditions have been met:

- Approximately 231 BICR PFS events have occurred across the MEDI4736 + tremelimumab and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (72% maturity) AND
- **CCI** to the study

The final (primary) OS analysis for superiority will be performed when the following conditions have been met:

- Approximately 225 OS events have occurred across the MEDI4736 + tremelimumab and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (70% maturity) AND
- Approximately 225 OS events have occurred across the MEDI4736 monotherapy and SoC treatment groups in patients with PD-L1 positive_{25%} tumors (70% maturity)

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment group. 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 for the corresponding treatment group.

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

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS, the PD-L1 positive_{25%} and PD-L1 positive_{1%} analysis sets. PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized on the Safety Analysis Set.

All outputs will be summarized by treatment group for all randomized patients (ITT) and for all randomized patients in the PD-L1 positive_{25%} and PD-L1 positive_{1%} analysis sets, and where required, for all randomized patients within the PD-L1-low/negative analysis set.

Results of all statistical analysis will be presented using appropriately sized confidence intervals (CIs) and 2-sided p-values, unless otherwise stated.

The following table (Table 10) details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint.

Table 10 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Progression-free survival	<p><u>Stratified log-rank tests for:</u></p> <p>Co-Primary analyses using BICR RECIST 1.1 assessments:</p> <ul style="list-style-type: none"> - MEDI4736 + tremelimumab versus SoC for PD-L1 positive_{25%} population (stratified only for histology) <p>Secondary analysis using BICR RECIST 1.1 assessments:</p> <ul style="list-style-type: none"> - MEDI4736 monotherapy versus SoC for PD-L1 positive_{25%} population (stratified only for histology) - MEDI4736 + tremelimumab versus SoC for PD-L1 positive_{1%} population - MEDI4736 + tremelimumab versus SoC (ITT population) - - - MEDI4736 + tremelimumab versus MEDI4736 monotherapy (ITT population) - MEDI4736 + tremelimumab versus MEDI4736 monotherapy for PD-L1 positive_{25%} population (stratified only for histology) <p>Sensitivity analyses using Investigator assessments (RECIST 1.1)</p> <p>Sensitivity analysis based on RECIST 1.1 modified for confirmation of progression using BICR assessments</p> <p>CCI</p>

Endpoints analyzed	Notes
Overall survival	<p><u>Stratified log-rank tests for:</u></p> <p>Co-primary analysis</p> <ul style="list-style-type: none"> - : MEDI4736 + tremelimumab versus SoC for PD-L1 positive_{25%} population (stratified only for histology) - MEDI4736 monotherapy versus SoC for PD-L1 positive_{25%} population (stratified only for histology) <p>Secondary analysis:</p> <ul style="list-style-type: none"> - MEDI4736 + tremelimumab versus SoC for PD-L1 positive_{1%} population MEDI4736 + tremelimumab versus SoC ITT population) - MEDI4736 + tremelimumab versus MEDI4736 monotherapy (ITT population) - MEDI4736 + tremelimumab versus MEDI4736 monotherapy for PD-L1 positive_{25%}, population (stratified only for histology)
Objective response rate	<p><u>Logistic regression for:</u></p> <p>Secondary analysis for the ITT, PD-L1 positive_{25%}, PD-L1 positive_{1%}, populations using BICR RECIST 1.1 assessments</p> <p>CCI</p> <p>CCI</p>
Duration of response	<p><u>Analysis methods as described by Ellis et al 2008 for:</u></p> <p>Secondary analysis using BICR assessments (RECIST 1.1)</p>
Proportion of patients alive and progression free at 12 months	<p>Hazard ratio using the Kaplan Meier estimates of progression free survival at 12 months (following method described by Klein et al 2007)</p>
Time from randomization to second progression	<p><u>Stratified log-rank test</u></p>
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	<p><u>Stratified log-rank test</u></p>

Multiple testing strategy

In order to strongly control the type I error at 5% 2-sided, a multiple testing procedure (MTP) with gatekeeping strategy will be used across the co-primary endpoints (PFS, OS), analysis populations (ITT, PD-L1 positive_{25%} and PD-L1 positive_{1%}, and treatment regimens (MEDI4736 + tremelimumab, MEDI4736 monotherapy, and SoC). If the higher level hypothesis in the MTP is rejected for superiority, the following hypothesis will then be tested as shown in [Figure 5](#).

Hypotheses will be tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses will be tested in a pre-defined order as outlined in Figure 5. According to alpha (test mass) splitting and alpha recycling, the test mass that becomes available after each rejected hypothesis is recycled to secondary hypotheses not yet rejected. Since OS is tested at multiple timepoints (ie, 2 interim analyses and final analysis), the OS tests that for the same comparison/population (ie, shown in 1 box in the MTP) will be considered as 1 test family. As long as one test in the family can be rejected, the family is rejected thus the assigned total alpha to the family can be recycled to next MTP level. This testing procedure stops when the entire test mass is allocated to non-rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), among all key hypotheses. Figure 5 shows the multiple testing framework.

The details on the alpha-exhaustive recycling procedure will be provided in the Statistical Analysis Plan.

The co-primary endpoint OS is tested at 2 interim and a final timepoint. The alpha level allocated to OS will be controlled at the interim and primary time points by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends upon the proportion of information available. The first OS interim analysis for superiority will occur at the primary PFS analysis, when it is expected that approximately 68% of the target death events may occur.

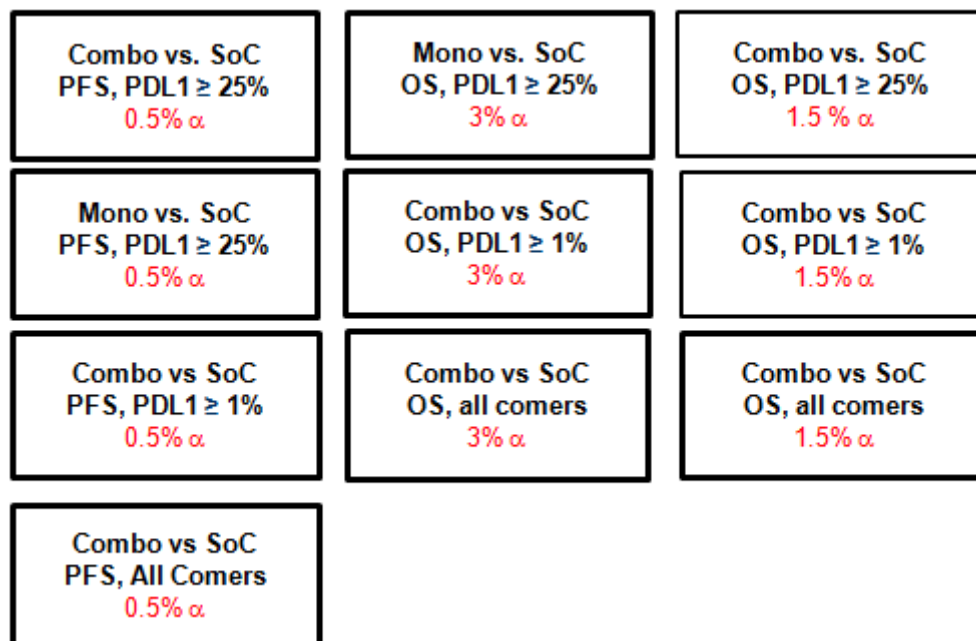
The second OS interim will subsequently be performed at approximately 80% of the target death events, with the primary OS analysis performed when 225 deaths have accumulated. If exactly 68% and 80% of the target events in the PD-L1 positive_{25%} patients are available at the time of the first and second interims analyses, respectively (ie, 152/225 and 180/225 deaths have occurred), with overall 2-sided alpha levels of 0.015 and 0.03 respectively for the comparisons of MED14736 + tremelimumab versus SoC MED14736 monotherapy versus SoC, the 2-sided alpha level to be applied for the interim and final analyses would be 0.0023, 0.0049 and 0.0132 for the comparison of MED14736 + tremelimumab versus SoC and 0.0062, 0.0113 and 0.0258 for the comparison of MED14736 monotherapy versus SoC.

If the interim or final analyses indicate superiority in OS for either monotherapy or combination therapy in PD-L1 positive_{25%}, then subsequent analyses of secondary OS endpoints will be performed in accordance with the hierarchical testing strategy. A separate Lan DeMets (O'Brien Fleming) spending function will be used to determine the alpha levels at the interim and final analyses for testing the PD-L1 positive_{1%} and the all-comers hypotheses.

If the interim results do not meet the criterion of stopping for superiority for a given hypothesis, then follow-up will continue until the final target number of OS events for that comparison has been observed, following which the hypothesis will be re-tested. If the hypothesis is then rejected, subsequent testing will continue hierarchically. The above testing

procedure will ensure strong control of the family-wise error rate (Glimm et al, 2010). Additional details of the multiple testing procedure will be provided in the statistical analysis plan.

Figure 5 Multiple testing procedures for controlling the type 1 error rate



Combo MEDI4736 + tremelimumab combination therapy; Mono MEDI4736 monotherapy; SoC Standard of care.

8.5.1 Analysis of the co-primary endpoints

8.5.1.1 Progression-free survival

The co-primary PFS analyses will be based on the programmatically derived RECIST 1.1 using the BICR tumor assessments. The co-primary analysis performed in the PD-L1 positive_{25%} population uses a stratified log-rank test adjusting for histology (squamous versus non-squamous) only. The effect of MEDI4736 + tremelimumab versus SoC treatment will be estimated by the HR together with its corresponding 99.5% CI and p-value.

The HR and its CI can be estimated from the Cox proportional hazards model (Cox 1972).

All of the secondary analyses will be performed using the same methodology as for the primary analyses described above, except in cases where the secondary analyses are

performed on the FAS or PD-L1 positive_{1%} population, in which case the stratification will also adjust for PD-L1 status ($\geq 25\%$, $< 25\%$).

Kaplan-Meier plots of PFS will be presented by treatment group, and by treatment group and PD-L1 tumor status subgroup, where appropriate. 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 each treatment.

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█ [Redacted]

- CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of PFS.

Unless there is a marked difference between the results of the statistical analyses of the PFS from the BICR data and that of the site Investigator tumor data, these subgroup analyses will only be performed on the PFS endpoint using the BICR data.

Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. An initial model will be constructed, containing treatment and the stratification factors alone, to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

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Additionally, for each subgroup, the HR (for the treatment comparisons of interest) and 95% CI will be calculated from a single model that contains treatment and subgroup factor. These will be presented on a forest plot including the HR and 95% CI.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

8.5.1.2 Overall survival

Co-primary OS in the PD-L1 positive_{25%} population will be analyzed using a stratified log-rank tests, using the same methodology as described for the co-primary PFS endpoint. The effect of MEDI4736 + tremelimumab versus SoC and MEDI4736 monotherapy versus SoC will be estimated by the HR together with its corresponding two-sided CI (98.5% for

MEDI4736 + tremelimumab versus SoC and 97% for MEDI4736 monotherapy versus SoC, adjusted for two interim analyses) and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment.

The boundaries (ie, adjusted alpha levels) for the treatment comparison at the interim and final analyses for OS will be derived based upon the exact number of OS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function (see Section 8.28.2).

Subgroup analyses will be conducted, as deemed appropriate, in the PD-L1 positive_{25%} analysis set comparing OS between MEDI4736 + tremelimumab versus SoC and MEDI4736 monotherapy versus SoC and in the PD-L1 positive_{1%} analysis set comparing OS between MEDI4736 + tremelimumab versus SoC using the same subgroups as specified for PFS. Similar subgroup analyses will be performed in the FAS for the comparison between MEDI4736 + tremelimumab versus SoC as deemed appropriate.

Impact of switching (crossover outside of this study) to immunotherapies (or other potentially active investigational agents) on OS analyses

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The decision to adjust and the final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. CCI [REDACTED]

8.5.2 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using the BICR tumor data. The ORR will be compared between MEDI4736 + tremelimumab versus SoC using logistic regression models adjusting for the same factors as the primary endpoint (PD-L1 tumor expression and histology, as appropriate). The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). This analysis will be performed in the PD-L1 positive_{25%}, PD-L1 positive_{1%} and ITT populations.. The analysis of the PD-L1 subgroup patients will be performed using a logistic regression model adjusting for only histology.

This analysis of ORR will be repeated using the results of the programmatically derived ORR using the site Investigator tumor data based upon RECIST 1.1 as a sensitivity analysis to confirm the results of the primary analysis derived from the eCRFs.

ORR by irRECIST 1.1 criteria using BICR assessments will also be reported in the ITT population.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). Overall visit response data will be listed for all patients. For each treatment group, best overall response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

8.5.3 Duration of response

In order to analyze the DoR between MEDI4736 + tremelimumab and SoC, the expected duration of response (EDoR) will be derived for each treatment group (Ellis et al 2008) using the BICR tumor data. The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients and provides an estimate based on all randomized patients. CCI

Additionally, descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment groups or p-value attached). This analysis will be performed in the PD-L1 positive_{25%}, PD-L1 positive_{1%} and ITT populations.

8.5.4 Proportion of patients alive and progression free at 12 months

The APF12 will be summarized (using the Kaplan-Meier curve) and presented by treatment group. APF12 will be compared between MEDI4736 + tremelimumab and SoC by using the

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This analysis will be performed in the PD-L1 positive_{25%}, PD-L1 positive_{1%} and ITT populations.

8.5.5 Time from randomization to second progression

PFS2 is defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death. PFS2 in the ITT population will be analyzed using a stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of MEDI4736 + tremelimumab versus SoC will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

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A summary table of first subsequent therapies by treatment group will be provided, as well as response to first subsequent therapy by treatment group.

This analysis will be performed in the PD-L1 positive_{25%}, PD-L1 positive_{1%} and ITT populations.

8.5.6 Patient reported outcomes

8.5.6.1 EORTC QLQ-C30

Time to deterioration in the PD-L1 positive_{25%}, PD-L1 positive_{1%} and ITT populations will be analyzed using a stratified log-rank test, using the same methodology as described for the primary PFS endpoint.

The effect of MEDI4736 + tremelimumab versus SoC will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

A summary of the symptom improvement rate for each of the 3 symptom scales and the 5 individual symptom items will be produced. Similarly, a summary of QoL/function improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced.

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score and each functional domain will be reported by visit for each treatment

group. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal item (in terms of the proportion of patients in the categories of improvement, no change, and deterioration as defined in Section 8.4.4.1) will also be produced for each treatment group.

8.5.6.2 EORTC QLQ-LC13

Time to deterioration in the PD-L1 positive_{25%}, PD-L1 positive_{1%} and ITT populations will be analyzed using a stratified log-rank test, using the same methodology as described for the primary PFS endpoint.

The effect of MEDI4736 + tremelimumab versus SoC will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

A summary of the symptom improvement rate for each of the 6 individual symptom items will be produced.

Summaries of original and change from baseline values of each symptom (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, other pain) and each treatment-related side effect (sore mouth, dysphagia, peripheral neuropathy and alopecia) will be reported by visit for each treatment group. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal symptom item (in terms of the proportion of patients in the categories of improvement, no change, and deterioration as defined in Section 8.4.4.2) will also be produced for each treatment group.

For PRO symptoms and HRQoL endpoints, the overall type I error (5% 2-sided) will be controlled across the 5 primary PRO measures of cough, dyspnea, and pain as assessed by the EORTC QLQ-LC13 and fatigue and appetite loss as assessed by the EORTC QLQ-C30 using the Bonferroni-Holm procedure (Holm 1979).

The physical functioning and overall health status domains of the EORTC QLQ-C30 are furthermore pre-specified endpoints of interest.

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8.5.8 Safety data

Safety and tolerability data will be presented by treatment group using the safety population.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment group and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining retreatment with MEDI4736 + tremelimumab will be produced separately, if required.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to MEDI4736 + tremelimumab, MEDI4736 monotherapy, and SoC will be summarized. Time on study, MEDI4736 + tremelimumab, MEDI4736 monotherapy, and SoC, dose delays/interruptions and dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

8.5.9 Pharmacokinetic data

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

8.5.10 Immunogenicity analysis

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

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

8.5.11 Pharmacokinetic/Pharmacodynamic relationships

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8.5.12 Biomarker data

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8.5.13 Interim analysis

Interim monitoring for safety will be conducted by the IDMC. Details of the plan and communication process will be provided in the statistical analysis plan and the IDMC charter.

In addition, two OS interim analyses will be performed for superiority; the first one at the time of the primary PFS analysis and the second one when approximately 80% of the final number of deaths has been reached. These analyses will be performed by an IDMC.

The Lan DeMets spending function that approximates an O'Brien Fleming approach will be used to account for multiplicity introduced by including the 2 interim analyses for superiority ([Lan and DeMets 1983](#)).

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If the interim analyses indicate superiority in the PD-L1 positive_{25%} population, then subsequent analyses of the further secondary endpoints will be performed in accordance with the hierarchical multiple testing strategy.

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9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is enrolled in the study, an AstraZeneca representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and train them in any study-specific procedures and IVRS/IWRS, WBDC, and any electronic PRO systems to be utilized.

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

The AstraZeneca representative will be available between visits if the Investigators or other staff at the centers 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 Direct access to source data in Japan

The Head of the study site and the Principal Investigator/Investigator will cooperate for monitoring and audit by AstraZeneca and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor will verify data from the eCRFs against source data before the Principal Investigator signs the eCRFs to ensure accuracy and completeness of documentation and ensure that the Principal Investigator has submitted the eCRFs to AstraZeneca.

9.2.3 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 clinical study protocol and the CSA, the terms of clinical study protocol 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 any patients are enrolled.

9.2.4 Archiving of study documents

The Investigator will follow 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 AstraZeneca when recruitment is complete.

The study is expected to start in Q3 2015 and 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 involving MEDI4736.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by a chosen vendor according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the chosen vendor.

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

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, validated, signed, and locked, a clean file will be declared. Any treatment-revealing data may be added thereafter, 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 management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping database or other appropriate secure system within AstraZeneca and/or a third party contracted to work with AstraZeneca to analyze samples. The results from this genetic research may be reported in the CSR for the main study or in a separate report, as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Data associated with human biological samples

Data associated with human 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. The applicable regulatory requirements in Japan are “Good Clinical Practice for Trials on Drugs” (Ministry of Health, Labor, and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications).

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.

AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient’s identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient’s medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An 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 should be approved, according to local regulations.

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

AstraZeneca will provide regulatory authorities, ECs/IRBs, and Principal Investigators safety updates or reports according to local requirements.

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

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 each patient is notified that he or she is 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 a 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.

For sites in Japan only

If any new information on the study medication becomes available that may influence the decision of the patient to continue the study, the Investigator should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue the participation in the study. In addition, if the Investigator deems it necessary to revise the ICF, he or she should revise it immediately (refer to Section 10.5).

The Investigator should re-explain to the patients using the updated ICF even if the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

10.5 Changes to the protocol and informed consent form

For sites outside Japan

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 clinical study protocol).

The amendment is to be approved by the relevant EC/IRB and, if applicable, 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 to determine if data were recorded, analyzed, and accurately reported according to the protocol, GCPs, ICH guidelines, 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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Document Title:	D419AC00001 Clinical Study Protocol Version 8	
Document ID:	Doc ID-003403622	
Version Label:	5.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	Signed by	Meaning of Signature
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