Revised Clinical Study Protocol

Drug Substance	Durvalumab (MEDI4736)
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A Phase III, Open-label, Randomised, Multi-centre, International Study of MEDI4736, Given as Monotherapy or in Combination with Tremelimumab, Determined by PD-L1 Expression, Versus Standard of Care in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV) who Have Received at Least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen and Do Not Have Known EGFR TK Activating Mutations or ALK Rearrangements (ARCTIC)

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EudraCT number: 2014-000338-46

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12 Feb 2018

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
01	18 June 2014		
02	28 July 2014		
03	29 August 2014		
04	27 March 2015		
05.1	30 December 2015		
06	31 August 2016		
07	19 September 2017		
08	08 January 2018		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
01	05 February 2015		
02	17 June 2015		

PROTOCOL SYNOPSIS

A Phase III, Open-label, Randomised, Multi-centre, International Study of MEDI4736, Given as Monotherapy or in Combination with Tremelimumab, Determined by PD-L1 Expression, Versus Standard of Care in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV) who Have Received at Least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen and Do Not Have Known EGFR TK Activating Mutations or ALK Rearrangements (ARCTIC)

International Coordinating Investigator

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Study centre(s) and number of patients planned

Approximately 1300 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC; Stage IIIB-IV) will be recruited, and approximately 610 patients randomised, at approximately 250 sites in North America, Latin America, Asia, Europe, Australia and New Zealand.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2015	III
Estimated date of last patient completed	Q4 2018	III

Objectives

This study will consist of 2 sub-studies: Sub-study A will address the research hypotheses for MEDI4736 monotherapy in patients with programmed death ligand 1 (PD-L1)-positive tumours (where positive is defined as ≥25% of tumour cells with membrane staining [proprietary PD-L1 immunohistochemistry assay; Ventana Medical Systems, Inc]), and Sub-study B will address the research hypotheses for MEDI4736 plus tremelimumab (MEDI4736+tremelimumab) in patients with PD-L1-negative tumours (ie, those with <25% of tumour cells with membrane staining).

The research hypotheses on the respective sub-studies will be assessed via the primary objectives in Sub-study A (NSCLC patients with PD-L1-positive tumours) and Sub-study B (NSCLC patients with PD-L1-negative tumours), which is to assess the efficacy of MEDI4736 and MEDI4736+tremelimumab treatment compared with Standard of Care in terms of overall survival (OS) and progression free survival (PFS).

Secondary efficacy objectives in each of the 2 sub-studies include evaluation of the proportion of patients alive at 12 months from randomisation (OS12), objective response rate (ORR), duration of response (DoR), the proportion of patients alive and progression free at 6 months from randomisation (APF6) and the proportion of patients alive and progression free at 12 months from randomisation (APF12), and the time from randomisation to second progression (PFS2). Other secondary objectives in each of the sub-studies include an assessment of safety and tolerability, pharmacokinetic (PK) exposure and immunogenicity, and patient reported outcomes. Exploratory objectives are also included.

Primary Objective:	**Outcome Measure:**
Sub-study A (PD-L1-positive population) To assess the efficacy of MEDI4736 monotherapy compared with Standard of Care in terms of OS and PFS Sub-study B (PD-L1-negative population) To assess the efficacy of MEDI4736+tremelimumab treatment compared with Standard of Care in terms of OS and PFS	OS[a] PFS using investigator assessments according to RECIST 1.1[a,b]

a In each of the Sub-studies A and B the assessment of PFS and OS will be considered co-primary objectives.
b The co-primary analysis of PFS will be based on programmatically-derived PFS based upon investigator assessment.
OS Overall survival; PD-L1 Programmed death ligand 1; PFS Progression free survival; RECIST Response Evaluation Criteria In Solid Tumours.

The following are the secondary objectives in Sub-study A (MEDI4736 monotherapy versus Standard of Care) and Sub-study B (MEDI4736+tremelimumab versus Standard of Care):

Secondary Objective:	**Outcome Measure:**
To further assess the efficacy in terms of: OS12, ORR, DoR, APF6, APF12 and PFS2	OS12 ORR using investigator assessments according to RECIST 1.1[a] DoR using investigator assessments according to RECIST 1.1[a] APF6 and APF12 using investigator assessments according to RECIST 1.1[a] PFS2 as defined by local standard clinical practice
To assess the safety and tolerability profile	Adverse events, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, haematology and urinalysis
To assess the PK of MEDI4736 and tremelimumab	Concentration of PK in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling)
To investigate the immunogenicity of MEDI4736 and tremelimumab	ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed])
To assess symptoms and health-related QoL using EORTC QLQ-C30 v3 and LC13	EORTC QLQ-C30: Time to symptom deterioration (fatigue, pain, nausea/vomiting, dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea). Time to QoL/function deterioration (physical function, role function, emotional function, cognitive function, social function and global health status/QoL) LC13: Time to symptom deterioration (dyspnoea, cough, haemoptysis, chest pain, arm/shoulder pain, other pain) Changes in World Health Organisation Performance Status will also be assessed
Sub-study B (PD-L1-negative population) To evaluate the efficacy of MEDI4736+tremelimumab treatment compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy	PFS[a], ORR[a] and DoR[a] using investigator assessments according to RECIST 1.1, and OS

a Analysis of ORR, DoR, APF6 and APF12 will be based upon investigator assessment.
ADA Anti-drug antibody; APF6 Proportion of patients alive and progression free at 6 months from randomisation; APF12 Proportion of patients alive and progression free at 12 months from randomisation; DoR Duration of response; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; LC13 Lung Cancer Module; ORR Objective response rate; OS12 Proportion of patients alive at 12 months from randomisation; PFS Progression free survival; PFS2 Time from randomisation to second progression; PK Pharmacokinetic(s); QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumours.

In Sub-study B, PFS in MEDI4736+tremelimumab arm will be compared to each of the MEDI4736 and tremelimumab monotherapy arms as part of the contribution of components

analysis. This analysis is planned to be performed when approximately 158 PFS events are observed in the MEDI4736+tremelimumab and tremelimumab monotherapy arms. However, for practical considerations, if this time is close to the time of the final PFS analysis, the contribution of components analysis will be conducted at the time of the PFS final analyses. This is considered a secondary objective of the study.

The following exploratory objectives will be addressed in Sub-studies A and B:

CCI [redacted]	[redacted]
[redacted]	[redacted]

AE Adverse event; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; IFN Interferon; IL Interleukin; ORR Objective response rate; OS Overall survival; PD-L1 Programmed death ligand 1; PDx Pharmacodynamic(s); PFS Progression free survival; PK Pharmacokinetic(s).

Study design

This study is a Phase III, randomised, open label, multi-centre study assessing the efficacy and safety of MEDI4736 versus Standard of Care in NSCLC patients with PD-L1-positive tumours, and the combination of MEDI4736+tremelimumab versus Standard of Care in NSCLC patients with PD-L1-negative tumours. The study will enrol male and female patients with locally advanced or metastatic NSCLC (Stage IIIB-IV), who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen for NSCLC. Patients with known epidermal growth factor receptor (EGFR) tyrosine kinase (TK) activating mutations and anaplastic lymphoma kinase (ALK) rearrangements are not eligible for the study (prospective testing is not planned within this study). Patients will be randomised in a 1:1 ratio in Sub-study A and a 3:2:2:1 ratio (MEDI4736+tremelimumab:MEDI4736:Standard of Care:tremelimumab) in Sub-study B.

The original study design intended to recruit 250 patients to Sub-study A. However, due to low patient accrual, the recruitment to Sub-study A was closed in Q1 2016 at which time 126 patients had been randomised. As a result, the analysis plan for Sub-study A was updated and is presented in Protocol Amendment 6.0, dated 31 August 2016.

Sub-study A (patients with PD-L1-positive tumours):

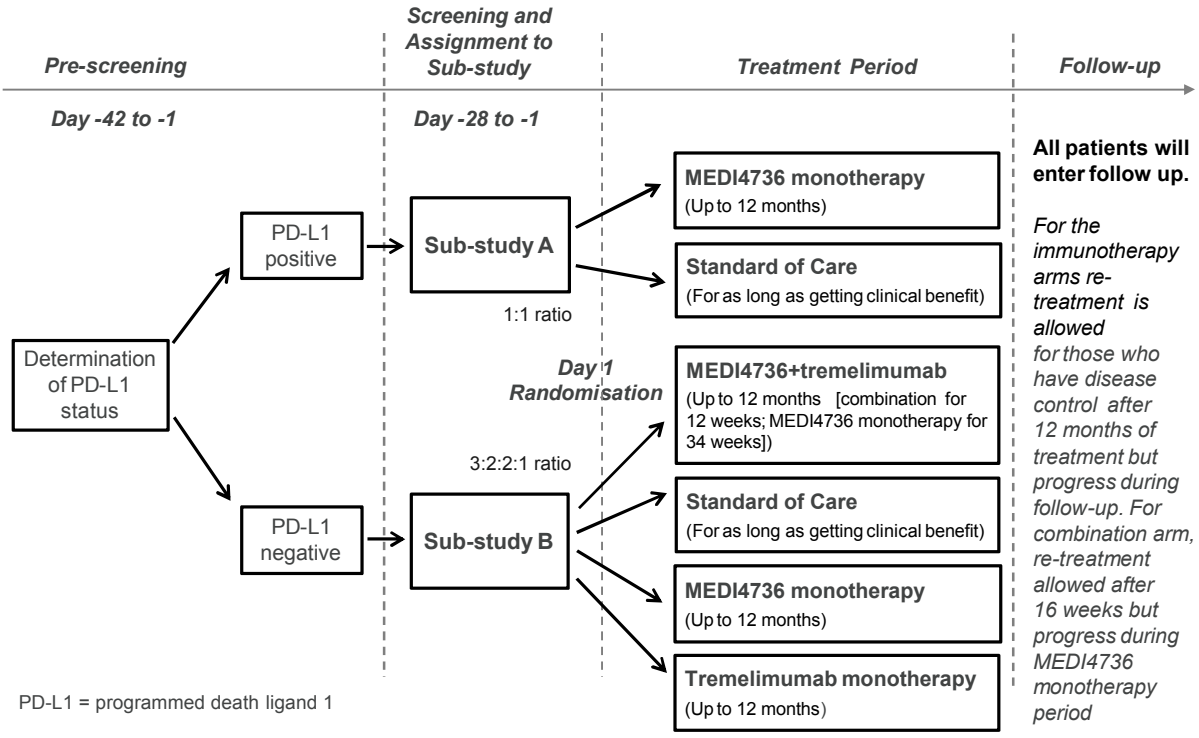
- MEDI4736 (10 mg/kg once every 2 weeks [Q2W] intravenously [iv] for up to 12 months) (approximately 60 patients)
- Standard of Care (restricted to erlotinib, gemcitabine or vinorelbine) (approximately 60 patients).
  - Erlotinib: 150 mg once daily, orally
  - Gemcitabine: 1000 mg/m^2 iv on Days 1, 8, and 15 of a 28-day cycle
  - Vinorelbine: 30 mg/m^2 iv on Days 1, 8, 15 and 22 of a 28-day cycle.

Sub-study B (patients with PD-L1-negative tumours):

- MEDI4736+tremelimumab (MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg once every 4 weeks [Q4W] iv for up to 12 weeks [4 doses]) then MEDI4736 alone (10 mg/kg Q2W iv, starting at Week 16, for 34 weeks [18 doses]) (180 patients)
- Standard of Care (see under Sub-study A) (120 patients)
- MEDI4736 (10 mg/kg Q2W iv for up to 12 months) (120 patients)
- Tremelimumab (10 mg/kg Q4W iv for 24 weeks then Q12W for 24 weeks) (60 patients).

The sub-studies may not run concurrently with the start and completion of recruitment potentially occurring at different time points. Assignment to the applicable sub-study will be preceded by the Pre-screening Period during which assessment of the patient's PD-L1 status, based on a tumour sample, will take place. After confirmation of PD-L1 status, patients will enter the main Screening Period within their assigned sub-study if it remains open for recruitment. The study design is shown in diagram form in Figure 1.

Figure 1 Study design schema



Details for all study procedures at Pre-screening, at Screening, during the Treatment Period and Follow-up are described within the applicable sections of the study protocol.

PD-L1 expression will be determined for all patients prior to randomisation. Patients will be assigned to Sub-study A and Sub-study B, respectively based on PD-L1 tumour expression status (PD-L1 positive versus PD-L1 negative [based on an archival tumour sample or a recent tumour biopsy]). Patients will be stratified at randomisation based on the Standard of Care treatment that they would be administered if randomised to the Standard of Care arm (2 categories: gemcitabine/vinorelbine versus erlotinib) and histology (2 categories: squamous versus all other).

The primary objective of this study is to assess the efficacy of MEDI4736 monotherapy (patients with PD-L1-positive tumours) and MEDI4736+tremelimumab (patients with PD-L1-negative tumours) compared with Standard of Care in terms of OS and PFS (per RECIST 1.1 as assessed by the investigator).

For Sub-study B, an interim analysis for OS will be performed. The purpose of the OS interim analysis is to demonstrate superiority to support the primary objective in terms of OS.

For Sub-study B, a contribution of components analysis will be performed when approximately 158 PFS events are observed in the MEDI4736+tremelimumab and tremelimumab monotherapy arms. However, for practical considerations, if this time is close to the time of the final PFS analysis, the contribution of components analysis will be conducted at the time of the final PFS analysis. The purpose of this analysis is to compare the monotherapy and combination dosing regimens to determine if the combination therapy (ie, MEDI4736+tremelimumab) is more efficacious than each of the monotherapy arms. As these treatment comparisons are secondary and serve a different purpose to that of the primary comparisons, they are not included in the multiple testing procedure for the primary comparisons, and an alpha of 0.05 will be used for either PFS or OS without multiplicity adjustment.

If the contribution of components analysis is performed prior to the final PFS analysis and the MEDI4736+tremelimumab arm is superior to either of the monotherapy arms, then that monotherapy arm may be dropped from the study and all patients on that treatment will be discontinued. However, any patients on that treatment will have the opportunity to remain on treatment if they are gaining clinical benefit and if, after discussion with their treating physician, it is felt that this is the best treatment option for them.

Sub-study A: Treatment with MEDI4736 10 mg/kg will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a Q2W schedule for up to 12 months. Treatment should be discontinued prior to 12 months if there is confirmed progression of disease (PD) (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Patients who have discontinued treatment due to toxicity, symptomatic deterioration or who have commenced subsequent anti-cancer therapy will be followed up until confirmed disease progression or death (whichever occurs first). Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (partial response [PR] or complete response

[CR]) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Sub-study B: Treatment with MEDI4736 or tremelimumab monotherapy, or the combination of MEDI4736 plus tremelimumab will commence on Day 1 following randomisation after confirmation of eligibility. MEDI4736 will continue on a 10 mg/kg Q2W schedule when given as monotherapy for up to 12 months and tremelimumab when given as a monotherapy will continue on a 10 mg/kg Q4W schedule for 24 weeks then Q12W for a further 24 weeks. MEDI4736+tremelimumab in combination will be administered from Day 1 on a Q4W schedule up to 12 weeks (4 doses of MEDI4736 20 mg/kg and tremelimumab 1 mg/kg) after which MEDI4736 10 mg/kg alone will be administered on a Q2W schedule for 34 weeks starting at Week 16 (18 doses).

In the monotherapy arms, treatment should be discontinued prior to 12 months (MEDI4736 monotherapy) or 48 weeks (tremelimumab monotherapy) if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Patients who have discontinued treatment due to toxicity, symptomatic deterioration or who have commenced subsequent anti-cancer therapy will be followed up until confirmed disease progression or death (whichever occurs first).

Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

In the MEDI4736+tremelimumab combination arm, if a patient experiences PD, retreatment with the combination regimen (MEDI4736+tremelimumab) is allowed. Retreatment in the combination arm can only occur if PD, with or without confirmation, occurs during the MEDI4736 monotherapy portion or after completion of 12 months of therapy. During the retreatment period, the patient would resume MEDI4736 dosing at 20 mg/kg Q4W as during the initial induction period, along with 1 mg/kg of tremelimumab Q4W for 4 doses. Monotherapy with MEDI4736 would then resume at 10 mg/kg Q2W 4 weeks after the last combination dose is administered. Retreatment will continue as long as the investigator judges the patient is deriving clinical benefit.

Both Sub-study A and B: Treatment in the Standard of Care arm will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a 4-weekly schedule until PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent or other reasons to discontinue treatment occur.

Tumour assessments will be performed using computed tomography/magnetic resonance imaging. The baseline assessment should be performed within the 28 days prior to randomisation. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks for the first 48 weeks (relative to the date of randomisation) then every

12 weeks thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment and/or subsequent therapy). An exception would be those patients with confirmed PD that continue to receive MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab at the discretion of the investigator (after consultation with the sponsor); these patients can receive treatment for a maximum of 12 months during the initial treatment period but for as long as the investigator judges they are gaining clinical benefit during the retreatment phase, and will have scans every 8 weeks until study treatment is stopped, or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST and other assessments per local standard of care.

A confirmatory scan is required following the initial demonstration of PD preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD, unless the patient will be entering retreatment, whereby a confirmatory PD scan is not required. In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study treatment until progression has been confirmed. In the Standard of Care arm, it is at the investigator's discretion if a patient with uncertain PD continues treatment until PD is confirmed; however, a confirmatory scan is required for all patients in the Standard of Care arm even if a subsequent treatment is started. 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.

Following completion or discontinuation of treatment, patients will enter a follow-up period. Once a patient has had objective progression recorded and has discontinued study drug, the patient will be followed up for survival status every 2 months until death, withdrawal of consent or the end of the study. Patients will also be assessed every 12 weeks for a second progression defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death.

Every effort should be made to obtain accurate follow-up information on patients whose PFS and OS data were not accurately recorded. For example, in the case of PFS, the local investigator could provide their clinical assessment of progression if care is transferred elsewhere, and for OS an effort should be made to continue to follow and use death registries where necessary.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be convened and will meet approximately 6 months after the study has started or 20 patients have been randomised to the combination arm on Sub-study B (whichever comes 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. The IDMC will also review:

- The interim analysis for OS on Sub-study B
- The contribution of components analysis for the immunotherapy arms if this analysis occurs before the primary PFS analysis.

All patients who receive a dose of study treatment will be evaluated for safety and tolerability. Enrolment will continue unless there is an unexpected safety concern. The study may be adjusted or suspended depending on the IDMC review outcome.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

Target patient population

Male or female patients aged 18 years or older with histologically-documented or cytologically-documented Stage IIIB/Stage IV NSCLC (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease). Patients must have received at least 2 prior systemic treatment regimens to be eligible including a platinum-based chemotherapy regimen. Patients with known EGFR TK activating mutations and ALK rearrangements are not eligible for the study. Patients must have WHO Performance Status of 0 or 1.

PD-L1 expression will be determined for all patients prior to randomisation. Patients with positive PD-L1 tumour expression status are eligible for Sub-study A, while patients with negative PD-L1 tumour expression status are eligible for Sub-study B.

Investigational product, dosage and mode of administration

MEDI4736 monotherapy arm (Sub-study A or Sub-study B) will receive MEDI4736 10 mg/kg via a 60-minute iv infusion Q2W (±3 days) for up to 12 months.

MEDI4736+tremelimumab arm (Sub-study B) will receive MEDI4736 20 mg/kg via a 60-minute iv infusion plus tremelimumab 1 mg/kg via a 60-minute iv infusion Q4W (±3 days) for 12 weeks then MEDI4736 10 mg/kg alone via a 60-minute iv infusion Q2W for a further 34 weeks.

Tremelimumab monotherapy arm (Sub-study B) will receive tremelimumab 10 mg/kg via a 60-minute iv infusion Q4W (±3 days) for 24 weeks then Q12W (±3 days) for a further 24 weeks.

Standard of Care, dosage and mode of administration

In both Sub-study A and B patients randomised to the Standard of Care arm will receive one of the following treatments based on investigator choice:

Gemcitabine

Gemcitabine should be administered at a dose of 1000 mg/m^2 iv over 30 minutes on Days 1, 8, and 15 (±3 days) of a 28-day cycle.

Vinorelbine

Vinorelbine should be administered at a dose of 30 mg/m^2 iv on Days 1, 8, 15 and 22 (±3 days) of a 28-day cycle.

Erlotinib

Erlotinib should be administered at a dose of 150 mg once daily as a tablet for oral administration taken at least 1 hour before or 2 hours after the ingestion of food.

Duration of treatment

MEDI4736 monotherapy arm

Treatment with MEDI4736 10 mg/kg will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a Q2W schedule for up to 12 months. The final administration of MEDI4736 will be at the Week 50 visit.

Disease progression that occurs while on treatment requires confirmation. In the absence of clinically significant deterioration, the investigational site is advised to continue the patient on study treatment until progression has been confirmed. If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

Treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur.

Tremelimumab monotherapy arm

Treatment with tremelimumab 10 mg/kg will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a Q4W schedule for 24 weeks then Q12W for a further 24 weeks.

Disease progression that occurs while on treatment requires confirmation. In the absence of clinically significant deterioration, the investigational site is advised to continue the patient on study treatment until progression has been confirmed. If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

Treatment should be discontinued prior to 48 weeks if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur.

MEDI4736+tremelimumab arm

Treatment with MEDI4736 (20 mg/kg) plus tremelimumab (1 mg/kg) will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a Q4W schedule for 12 weeks (4 doses of each). After 4 doses, tremelimumab will be stopped and treatment with MEDI4736 (10 mg/kg) will continue on a Q2W schedule, starting at Week 16, for 34 weeks (18 doses). The final administration of MEDI4736 on the MEDI4736+tremelimumab arm will be at the Week 50 visit.

In the combination arm, patients who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 4th cycle (Week 16, 4 weeks after the last dose of combination treatment) will continue with the planned treatment for this arm, ie, MEDI4736 10 mg/kg Q2W. If patients should experience PD (according to RECIST 1.1), with or without confirmation, during the MEDI4736 monotherapy treatment, retreatment with the combination regimen may begin.

Any patient who is restarting the combination treatment regimen will adhere to the same treatment guidelines followed during the initial treatment period (same treatment, same length and frequency of treatment, same assessments schedule). Patients may only restart the treatment once.

Treatment should be discontinued prior to 50 weeks if there is confirmed PD during the initial combination regimen (ie, during the first 4 cycles) or following the retreatment phase (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur.

Rules for treatment discontinuation, interruption and retreatment option for both MEDI4736 and tremelimumab monotherapy arms, and MEDI4736+tremelimumab arm

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period will enter follow-up. When these patients experience evidence of PD, with or without confirmation, during follow-up and meet the criteria for treatment in the setting of PD, they will be given the option to restart their assigned immune-mediated cancer treatment (ie, MEDI4736 monotherapy, tremelimumab monotherapy or combination MEDI4736+tremelimumab) for as long as the investigator judges they are gaining clinical benefit with the same treatment guidelines followed during the initial 12-month treatment period. Patients should have a baseline tumour assessment within 28 days before restarting their assigned immune-mediated cancer treatment; all further scans should occur every 8 weeks (relative to the date of restarting treatment) until study treatment is stopped. Only patients who the investigator determines do not have any significant, unacceptable, or irreversible toxicities, or would continue to receive benefit from therapy can restart a second treatment upon PD.

Patients with confirmed progression in the MEDI4736 monotherapy or tremelimumab monotherapy arms cannot continue treatment or obtain retreatment if the progression occurred during dosing and after confirmed response (ie, the response and progression events both occurred while receiving active immune-mediated cancer treatment during the same treatment period).

Retreatment in the combination arm can only occur if PD, with or without confirmation, occurs during the monotherapy portion or after completion of 12 months of treatment. During the retreatment period, the patient would resume MEDI4736 20 mg/kg Q4W as during the initial induction period, along with tremelimumab 1 mg/kg Q4W for 4 doses. Monotherapy with MEDI4736 10 mg/kg Q2W would then resume at 4 weeks after the last dose of

combination treatment for as long as the investigator judges that the patient is gaining clinical benefit.

For patients in the MEDI4736 or tremelimumab monotherapy arms or the MEDI4736+tremelimumab arm who have a dose interruption due to toxicity at any point in the treatment period may resume treatment and complete the treatment period accordingly as per applicable treatment arm duration.

Patients who have confirmed PD during the initial treatment period in the MEDI4736 or tremelimumab monotherapy arms, or after restarting treatment and cannot continue to receive study drug, will enter follow-up.

Patients with confirmed PD that continue to receive MEDI4736 monotherapy, tremelimumab monotherapy or who are in the MEDI4736+tremelimumab arm as originally intended, at the discretion of the investigator (following consultation with the sponsor), can receive treatment for a maximum of 12 months/48 weeks accordingly during the initial treatment period but for as long as the investigator judges they are gaining clinical benefit if they are a re-treatment patient.

Standard of Care

Treatment in the Standard of Care arm will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a 4-weekly schedule until PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur.

Treatment through PD in the Standard of Care arm is at the investigator's discretion. In cases of unequivocal progression the investigator should discontinue treatment, where it is uncertain if disease has progressed the investigator should decide whether (if in the absence of clinically significant deterioration) to continue the patient on treatment until progression has been confirmed.

Note: For all patients who receive study treatment through disease progression (not allowed if there is confirmed PD while on treatment following a previous response [PR or CR] while on treatment to study drug) and patients who achieve disease control (ie, CR, PR or SD) and restart MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab upon evidence of PD (according to RECIST 1.1) during follow-up, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in the protocol. These patient informed consent documents will specify that treatment beyond initial evidence of PD or re-treatment following progression during follow up is not the standard of care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive treatment.

Outcome variable(s):

See Objectives.

Statistical methods

The primary objective of this study is to assess the efficacy of MEDI4736 treatment (Sub-study A being concerned with MEDI4736 monotherapy and Sub-study B being primarily concerned with MEDI4736+tremelimumab) compared with Standard of Care in terms of OS and PFS. Overall survival is defined as the time from the date of randomisation until death due to any cause. Progression free survival (per RECIST 1.1 as assessed by the investigator) will be defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Thus, the 2 co-primary endpoints in this study are OS and PFS. Sub-study A will be descriptive in nature with no statistical testing. To control for type I error in Sub-study B, an alpha of 0.04 will be used for the analysis of OS and an alpha of 0.01 will be used for the analysis of PFS. The study will be considered positive (a success) if either the PFS analysis results and/or the OS analysis results are statistically significant in Sub-study B.

Secondary efficacy variables include: OS12, ORR, DoR, APF6, APF12 and PFS2.

Efficacy data will be summarised and analysed on an Intent-to-Treat (ITT) basis and will compare the treatment arms on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the ITT population.

A total of 126 patients will be randomised 1:1 to MEDI4736 or Standard of Care (gemcitabine, vinorelbine or erlotinib) in Sub-study A and approximately 480 patients will be randomised 3:2:2:1 to MEDI4736+tremelimumab or Standard of Care or MEDI4736

monotherapy or tremelimumab monotherapy in Sub-study B. The randomisation (via an Interactive Voice/Web Response System) will be stratified separately on each sub-study based on the Standard of Care treatment that they would be administered (2 categories: gemcitabine/vinorelbine versus erlotinib) and histology (2 categories: squamous versus all other).

The primary PFS and interim OS analysis for superiority in Sub-study B (PD-L1-negative population) will be performed when approximately 244 PFS events have occurred from 300 patients (81% maturity) who have been randomised to the MEDI4736+tremelimumab and Standard of Care arms. Assuming the true average hazard ratio (HR) is 0.63 in PD-L1-negative population for PFS (corresponding to a 1.3-month improvement in median PFS from a control group median of 3 months), the PFS analysis will have 84% power to demonstrate a statistically significant difference for PFS, with a type I error of 0.01 (2-sided).

The OS analysis in Sub-study A (PD-L1-positive population) will be performed when approximately 82 deaths have occurred from 126 patients (65% maturity).

The OS analysis in Sub-study B (PD-L1-negative population) will be performed when approximately 205 deaths have occurred from the 300 patients (68% maturity) who have been randomised to MEDI4736+tremelimumab and Standard of Care. Assuming the true average HR is 0.63 in PD-L1-negative population for OS (corresponding to a 4.4-month improvement in median OS from a control group median of 7 months), this analysis will have 89% power to demonstrate a statistically significant difference for OS, with an overall type I error of 0.04 (2-sided).

The boundaries for the treatment comparison at the interim and final analysis for OS on Sub-study B 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.

For Sub-study B, a contribution of components analysis will be performed when approximately 158 PFS events are observed in the MEDI4736+tremelimumab and tremelimumab monotherapy arms. However, for practical considerations, if this time is close to the time of the final PFS analysis, the contribution of components analysis will be conducted at the time of the final PFS analysis. The MEDI4736+tremelimumab versus tremelimumab monotherapy treatment comparison is the primary comparison. The MEDI4736+tremelimumab versus MEDI4736 monotherapy treatment comparison will also be performed at this time. As these treatment comparisons are secondary and serve a different purpose to that of the primary comparisons, they are not included in the multiple testing procedure for the primary comparisons, and an alpha of 0.05 will be used for either PFS or OS without multiplicity adjustment.

If the contribution of components analysis is performed prior to the final PFS analysis, the interim analyses for superiority of the MEDI4736+tremelimumab arm versus each monotherapy arm may be used to guide decisions on whether to discontinue either monotherapy arm or to continue the study without modification.

All interim analyses will be assessed by an IDMC.

Overall survival will be analysed in Sub-study B using a stratified log-rank test adjusting for Standard of Care therapy type (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other). The effect of treatment will be estimated by the HR together with its corresponding ([1-adjusted alpha] x 100)% CI (for the primary treatment comparison in each sub-study) and p-value for the ITT population. Note that the alpha-adjusted CI and p-value will only be generated on Sub-study B. The HR and 95% CI will be generated on Sub-study A.

Progression free survival based upon the site investigator data will be analysed using the same methodology as described for the OS analyses. The HR and 95% CI will be generated on Sub-study A. The effect of treatment will be estimated by the HR, together with its corresponding 99% CI (for the primary treatment comparison in each sub-study) and p-value for the ITT population, for Sub-study B only.

Safety data will be summarised descriptively and will not be formally analysed.

End of Analysis Portion of Study

At the time of the final DCO, the analysis portion of the clinical study will have been completed and all patients remaining in the study will be considered to have completed the analysis portion of the study.

Patients in OS follow-up (progressed and have completed treatment) will be considered to have completed the study. Patients in progression-free follow up (patients who have completed treatment and have not progressed and who are still potentially eligible for retreatment) may decide to continue in the study in progression-free follow up. These patients would therefore remain eligible for possible future re-treatment upon progression if they meet re-treatment criteria and the investigator judges that the patient will gain clinical benefit. Patients already receiving re-treatment at the time of final DCO for the study may continue receiving investigational product if the investigator judges that they are gaining clinical benefit.

Scans will be collected in accordance with local clinical practice. Patients in progression-free follow-up after the final DCO are to undergo sampling for local laboratory assessments in such a way that continued per-protocol re-treatment eligibility can be properly determined. For patients receiving re-treatment after final DCO, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3). All data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

For patients who either continue to receive treatment or begin re-treatment after the time of the final DCO, investigators will report all serious adverse events (SAEs) to AstraZeneca/MedImmune patient safety until 90 days after investigational product is

discontinued. Following the final DCO, SAE reporting applies only to patients who are active on the drug and within 90 days post the last dose. In addition, in patients who are still in progression-free follow-up at the final DCO and who are eligible for future re-treatment (ie, the patient was randomised to investigational product, completed the initial 12 month treatment period and had SD, PR or CR at completion of 12 months of treatment), notification must be sent to QuintilesIMS if the patient dies (via the statement of death CRF) or if the patient goes onto receive another alternate systemic anti-cancer therapy and thus becomes ineligible for re-treatment.

In the event that a roll-over or safety extension study will become available, patients currently receiving treatment with study drug or patients in progression-free follow-up may be transitioned to such a study, and the current study would 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.

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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 (see definition in Section 6.4.1)
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF6	Proportion of patients alive and progression free at 6 months from randomisation
APF12	Proportion of patients alive and progression free at 12 months from randomisation
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BoR	Best objective response
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DCO	Data cut-off
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation or special term	Explanation
EDoR	Expected Duration of Response
EDTA	disodium edetate dihydrate
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire
EQ-5D	EuroQoL 5-dimension utility index
EQ-5D-5L	EuroQoL 5-dimension, 5-level health state utility index
ESMO	European Society of Medical Oncology
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTIH	First-Time-In-Human
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRA	Health Research Associates, Inc
HRQoL	Health Related Quality of Life
IASLC	International Association for the Study of Lung Cancer
IB	Investigator Brochure
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IMT	immunomodulatory therapy
INR	International normalised ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the investigator co-ordinating the investigators and/or activities internationally.
irAE	Immune-related adverse event
IRB	Institutional Review Board
ITT	Intent-to-Treat

Abbreviation or special term	Explanation
iv	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LC13	Lung Cancer Module; 13-item self-administered questionnaire from the EORTC for lung cancer
LIMS	Laboratory Information Management System
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro RNA
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
NE	Not evaluable
NSCLC	Non-small cell lung cancer
OAE	Other significant adverse event (see definition in Section 11.2.2)
ORR	Objective response rate
OS	Overall survival
OS12	Proportion of patients alive at 12 months from randomisation
PD	Progression of disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PDx	Pharmacodynamic(s)
PFS	Progression free survival
PFS2	Time from randomisation to second progression
PGx	Pharmacogenetic(s)
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcome(s)
PVC	Polyvinyl chloride
Q2W, Q4W, Q12W	Every 2 weeks, every 4 weeks, every 12 weeks
QoL	Quality of Life
QTc	QT interval corrected for heart rate

Abbreviation or special term	Explanation
R&D	Research and Development
RECIST	Response Evaluation Criteria In Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
SD	Stable disease
sPD-L1	Soluble programmed death ligand 1
SUSAR	Suspected Unexpected Serious Adverse Reaction(s)
T3	Triiodothyronine
T4	Thyroxine
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
T-cell	T lymphocyte
TMGs	Dose Modification and Toxicity Management Guidelines
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. INTRODUCTION

Investigators should be familiar with the current MEDI4736 and tremelimumab Investigator Brochures (IB).

1.1 Background

1.1.1 Non-small cell lung cancer

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (GLOBOCAN 2008). 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 Le Chevalier 2005).

Despite advances in the diagnosis, imaging, staging and treatment of NSCLC, the estimated overall 5-year survival for patients in Europe continues to be low (11%) (D'Addario et al 2010). Once patients have treatment failure following initial therapy, the outlook for those with refractory advanced NSCLC is extremely poor, with response to further systemic treatment of <10% (GLOBOCAN 2008, Hanna et al 2004) and median survival of approximately 6 months.

Common third-line treatment for NSCLC in major global markets includes: vinorelbine (NAVELBINE®), tyrosine kinase inhibitors (TKIs such as erlotinib [TARCEVA®] and gefitinib [IRESSA®]), pemetrexed (ALIMTA®), and docetaxel (TAXOTERE®) for non-squamous NSCLC, and vinorelbine, TKIs, gemcitabine and docetaxel (TAXOTERE®) for squamous NSCLC (Decisions Resources 2013). For these patients, clinical trials, experimental treatment, or best supportive care are among the treatment options (Azzoli et al 2009, Syrigos et al 2011).

1.1.2 Immunotherapies

The immune system can identify tumour-associated antigens and eliminate the cancerous cells expressing them and thus plays an important role in preventing and combating the growth of tumours. This process of tumour immune surveillance is believed to result in a co-evolution of the tumour and immune response termed immunoediting, which is thought to follow 3 stages (Swann and Smyth 2007).

- During the initial phase of elimination, the innate and adaptive immune systems detect and eliminate tumour cells. Elimination can result in complete clearance of tumour cells as is seen in rare cases of spontaneous regression of melanoma (Kalialis et al 2009).

- However, if elimination is incomplete, the immune system and tumour may enter a state of equilibrium. During this second phase of immunoediting, the immune response selectively eliminates susceptible tumour cells and may prevent tumour progression. As the equilibrium phase persists, the tumour may evolve mechanisms to avoid or attenuate the immune response.

- The emergence of tumour cells with reduced immunogenicity or enhanced immunosuppressive mechanisms leads to the escape phase of immunoediting. During the escape phase, many factors may contribute to the failure of the immune system to control tumour growth including the expression of immune-inhibitory molecules, presence of immunosuppressive regulatory T lymphocytes (T-cells) or immunosuppressive cytokines within the tumour microenvironment, and down-regulation of major histocompatibility molecules and tumour antigens leading to reduced antigen presentation and recognition.

Blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has also shown promising clinical activity. Ipilimumab binds to CTLA-4 and prevents the interaction of CTLA-4 with cluster of differentiation (CD) 80 and CD86, resulting in enhanced T-cell activation and proliferation (Lipson and Drake 2011). Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval in 2011 for the treatment of metastatic melanoma and is currently under investigation for several other malignancies.

PD-L1 (B7 homolog 1 [B7-H1], CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T-cells, B lymphocytes (B-cells), dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various nonhaematopoietic cells (Keir et al 2008). The normal function of PD-L1 is to regulate the balance between T-cell activation and tolerance through interaction with 2 receptors, programmed death 1 (PD-1, CD279) and CD80 (B7-1). PD-L1 is also expressed by tumours and acts at multiple sites to help tumours evade detection and elimination by the host immune system. In the lymph nodes, PD-L1 on antigen presenting cells binding to PD-1 (CD279) or CD80 (B7-1) on activated T-cells, delivers an inhibitory signal to the T-cell (Keir et al 2008, Park et al 2010). Likewise, binding of CD80 on antigen presenting cells to PD-L1 on T-cells leads to inhibitory signalling in the T-cell. These and bidirectional interactions between CD80 and PD-L1, expressed on both antigen presenting cells and T-cells, lead to further inhibition of T-cell activation. These interactions result in reduced T-cell activation and fewer activated T-cells in the circulation. In the tumour microenvironment, PD-L1 expressed on tumour cells binds to PD-1 on activated T-cells reaching the tumour. This delivers an inhibitory signal to those T-cells, preventing them from

killing the target tumour cells, and thus protecting the tumour from immune elimination (Zou and Chen 2008).

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancer. In a number of these cancers, including lung (Mu et al 2011), renal (Krambeck et al 2007, Thompson et al 2005, Thompson et al 2006), pancreatic (Loos et al 2008, Nomi et al 2007, Wang et al 2010), and ovarian cancers (Hamanishi et al 2007), the expression of PD-L1 is associated with reduced survival and an unfavourable prognosis. In ovarian cancer, for example, the 5-year survival rate in patients with low levels of PD-L1 was 80.2%, compared with 52.6% in patients with high levels of PD-L1 (Hamanishi et al 2007). In lung cancer, only 20% of patients with tumours expressing PD-L1 survived for more than 3 years, compared with 49% of patients with tumours lacking PD-L1 (Mu et al 2011). Based on these data, and on data for expression of PD-L1 on the surface of human tumours generated using proprietary immunohistochemistry methods for assessment, MEDI4736 has the potential to affect multiple types of solid tumours, including those with a high incidence rate and some less common types with limited treatment options and poor outcomes.

The levels of tumour-infiltrating cells, and more specifically cytotoxic T-cells, have been correlated to improved prognosis in a number of cancers including colorectal, melanoma, and lung cancers (Pagès et al 2010), suggesting that an anti-tumour immune response is beneficial to patients. In vitro, an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of anti-tumour T-cells (Blank et al 2006). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumour immune responses in patients with cancer. Results of several preclinical studies using mouse tumour models support this hypothesis, where antibodies directed against PD-L1, or its receptor PD-1, showed anti-tumour activity (Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Zhang et al 2008).

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, interferon [IFN]-γ) production in vitro in whole blood or peripheral blood mononuclear cells 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-tumour activity in animal models, including killing of established murine solid tumours and induction of protective anti-tumour immunity (see current tremelimumab IB). 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-tumour activity in patients with solid tumours.

1.1.2.1 Clinical data for agents targeting PD-1 and PD-L1

A Phase I clinical study of the anti-PD-1 antibody nivolumab (BMS-936558/MDX-1106) was conducted in 39 patients (Brahmer et al 2010). No dose limiting toxicities (DLTs) were observed and a maximum tolerated dose (MTD) was not identified. Efficacy data for nivolumab indicate an objective response rate (ORR) of 19% for NSCLC patients with squamous histology and 15% for NSCLC patients with non-squamous histology (Brahmer et al 2013). In a large Phase I study of nivolumab in 296 patients, treatment-related adverse events (AEs) were observed at all dose levels studied (Topalian et al 2012). The most frequent treatment-emergent AEs of any grade observed during this study were fatigue (24%), rash (12%), diarrhoea (11%) and pruritus (10%). Immune-mediated AEs of ≥Grade 3 occurred in 6% of patients and included pneumonitis (1%), diarrhoea (1%), alanine aminotransferase (ALT) increased (1%), and aspartate aminotransferase (AST) increased (1%). Of note, 3 deaths due to pneumonitis were assessed as related to study drug.

MK-3475, another anti-PD-1 monoclonal antibody (mAb), is being evaluated in Phase I and II studies, with data from a study of 135 patients with advanced melanoma recently reported (Hamid et al 2013). Efficacy data for MK-3475 in NSCLC has indicated an ORR of 24% by immune-related response criteria (irRC) (21% by Response Evaluation Criteria in Solid Tumours [RECIST]) after 2 previous NSCLC treatment regimens. Preliminary median overall survival (OS) was 51 weeks (Garon et al 2013). The most frequent treatment-related AEs of any grade observed in the study of 135 patients with advanced melanoma recently reported by Hamid et al 2013 were fatigue (30%), rash and pruritus (21% each), diarrhoea (20%), myalgia (12%), headache, asthenia, nausea, and elevated AST (10% each). Grade 3 or higher treatment-related AEs were reported in 13% of patients and included rash (2%), pruritus, hypothyroidism, diarrhoea, abdominal pain, fatigue, decreased appetite, elevated AST and renal failure (1% each).

Clinical data have also been reported from a Phase I clinical study of the anti-PD-L1 antibody, BMS-936559 (MDX-1105). Preliminary data for BMS-936559 (MDX-1105) indicates an ORR of 8% for NSCLC patients with squamous histology and 11% for NSCLC patients with non-squamous histology. The most frequently observed treatment-related AEs of any grade were similar to those observed with BMS-936558 and included fatigue (16%), infusion-related reaction (10%), diarrhoea (9%), rash (7%), arthralgia (7%), pruritus (6%) and nausea (6%) (Brahmer et al 2012). Immune-mediated AEs of ≥Grade 3 occurred in 5% of patients. Pneumonitis was not reported in this study.

Data for MPDL3280A, another anti-PD-L1 antibody in development in NSCLC patients, was presented by L Horn at The World Conference on Lung Cancer 2013. These data showed an ORR in smokers of 26%; versus 10% in never smokers and 23% in patients with epidermal growth factor receptor (EGFR) wild type mutation status and 23% in patients who were EGFR mutation positive. Safety data from 171 patients enrolled in a Phase I study of MPDL3280A has also been presented (Herbst et al 2013). In this ongoing study, the most frequently reported AEs, regardless of causality, were fatigue (43%), cough (26%), diarrhoea (26%), nausea (25%), decreased appetite (25%), headache (25%), constipation (23%), dyspnoea

(23%), pyrexia (22%), arthralgia (19%), rash (18%), and insomnia (18%). Grade 3 or 4 treatment-related AEs were reported in 13% of patients. No DLTs were observed and an MTD was not identified.

Studies of other agents targeting the PD-1/PD-L1 pathway are also in early stage development with limited data available. CT-011 (an anti-PD-1 mAb), has been evaluated in a Phase I study in advanced haematologic malignancies (Berger et al 2008). In this study of 17 patients, CT-011 was well tolerated and no treatment-related toxicities were reported. No MTD was identified in this population. The most frequent AE was diarrhoea, which occurred in 2 patients.

1.1.2.2 Clinical data for agents targeting CTLA-4

Ipilimumab is currently approved for the treatment of unresectable or metastatic melanoma. Ipilimumab is being studied in a number of other cancer indications and in combination with various anti-cancer agents.

Ipilimumab has been studied in NSCLC in combination with either chemotherapy or in ongoing trials in combination with anti-PD-1/PD-L1 agents. Ipilimumab was studied in a randomised, double-blind, trial evaluating the efficacy and safety of ipilimumab in combination with paclitaxel/carboplatin compared to paclitaxel/carboplatin alone in previously untreated patients with lung cancer. In this study ipilimumab was given either concurrently or sequentially with the platinum doublet chemotherapy and was continued in a maintenance schedule (10 mg/kg every 3 months) after discontinuation of chemotherapy until progression or undue toxicity.

Ipilimumab showed promising results in this first-line NSCLC Phase II study. The median immune-related progression-free survival was 5.7 months for the phased ipilimumab arm versus 4.6 months for chemotherapy alone (hazard ratio [HR] = 0.72, p = 0.05) and 5.5 months for the concurrent ipilimumab arm versus 4.63 months for chemotherapy alone (HR = 0.81, p = 0.13. The main AEs were immune-related, such as hypophysitis, enterocolitis and hyperthyroidism. Phase III studies are ongoing (Lynch et al 2012).

In addition to the first-line NSCLC Phase II study, a Phase I trial examining the use of phased ipilimumab with platinum-based chemotherapy in Japanese patients demonstrated a response rate of 60% in 10 evaluable NSCLC patients (Nokihara H 2013).

Interim results were presented at the American Society of Clinical Oncology (ASCO) 2014 on a study of 2 different dosing regimens of ipilimumab in combination with nivolumab in 2 cohorts of squamous and non-squamous first-line NSCLC patients. Objective response rate ranged from 11 to 33% across the 4 different arms based on histology and dosing regimens. Progression free survival (PFS) rates at 24 weeks ranged from 20 to 51%. Grade 3 and 4 treatment-related events were reported in 49% of patients across the treatment arms (Antonia et al 2014 ASCO).

1.1.3 MEDI4736

Refer to the current MEDI4736 IB for a complete summary of non-clinical and clinical information; see Section 5.5.3 of this protocol for guidance on management of potential MEDI4736-related toxicities.

MEDI4736 is a human mAb of the immunoglobulin (Ig)G1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. MEDI4736 is developed as an immunomodulatory therapy (IMT) within the pharmaco-therapeutic group of the anti-neoplastic agents. The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1, expressed on cancer cells and a subset of leukocytes, with the PD-1 (CD279) and B7-1 (CD80) molecules on antigen-presenting cells and T-cells. By binding to PD-L1 on tumour cells, the mechanism of action of MEDI4736 includes stimulation/re-engagement of the patient's anti-tumour immune response.

MEDI4736 has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of July 2015, a total of 1883 patients have been enrolled and treated with MEDI4736 in 30 ongoing sponsor and collaborative clinical studies: 13 employing MEDI4736 as monotherapy and 17 as combination therapy. No studies have yet been completed.

The majority of the safety data currently available for MEDI4736 are based on the First-Time-in-Human (FTIH), single-agent study (Study CD-ON-MEDI4736-1108; referred to hereafter as Study 1108) in patients with advanced solid tumours. As of 14 July 2014, 393 patients enrolled in Study 1108 have received MEDI4736 at 10 mg/kg every 2 weeks (Q2W; either in the dose-escalation or dose-expansion phase of the study). Of these 393 patients, 331 (84.2%) had at least 1 AE (regardless of causality. Overall, the most frequently reported (≥10% of patients) AEs (all grades) were fatigue, nausea, dyspnoea, decreased appetite, constipation, diarrhoea, vomiting, cough, pyrexia, back pain, and rash.

Approximately half (48.1%) of these AEs were Grade 1 to 2 in severity and manageable by general treatment guidelines as described in the current MEDI4736 study protocols. Grade 3 or higher AEs were noted in 141 of 393 patients (35.9%). These events occurring in more than 1% of patients were dyspnoea (5.1%); increased gamma-glutamyltransferase (3.3%); fatigue, general physical health deterioration, increased AST, and back pain (2.3% each); anaemia and dehydration (1.8% each); and abdominal pain, vomiting, sepsis, syncope, sepsis, and hypotension (1.3% each).

Treatment-related AEs were reported for 162 of 393 patients (41.2%). The most frequently reported (≥2% of patients) treatment-related AEs (all grades) were fatigue (13.5%); nausea (8.4%); diarrhoea, decreased appetite, and rash (5.3% each); vomiting (4.8%); pruritus (4.1%); dyspnoea (3.8%); pyrexia (3.1%); hypothyroidism (2.8%); increased ALT, increased AST, and cough (2.5% each); myalgia (2.3%); and abdominal pain and dizziness (2.0% each). No DLTs have been reported.

A total of 229 serious adverse events (SAEs), regardless of causality, have been reported in 123 of 393 patients (31.3%) treated with 10 mg/kg MEDI4736 Q2W. The SAEs reported for 5 or more patients were dyspnoea, general physical health deterioration, pyrexia, abdominal pain, back pain, dehydration, pleural effusion, and sepsis.

The important potential risks, based on the mechanism of action of MEDI4736, as well as data from studies of relevant or similar therapies, include immune-mediated reactions, such as enterocolitis, dermatitis, hepatotoxicity, endocrinopathy, pneumonitis, and other events such as serious infections, infusion-related reactions, anaphylaxis or serious allergic reaction and immune complex disease.

Data presented at the European Society for Medical Oncology (ESMO) 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; drug-related AEs leading to discontinuation reported in 1% of patients; no drug-related colitis or hyperglycaemia of any grade and no Grade ≥3 pneumonitis were reported and no drug-related AEs leading to death were reported (Antonia et al 2014 ESMO).

Efficacy data on the NSCLC patients in Study 1108, presented at ESMO 2014 (cut-off date of 21 August 2014), showed a disease control rate 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 in patients with PD-L1 positive (≥25% of tumour cells with membrane staining for PD-L1) tumours (25%; 12 complete response [CR]/partial response [PR]; n=48) compared to patients with PD-L1 negative tumours (10%; 7 CR/PR; n=74) (Antonia et al 2014 ESMO). Updated safety and efficacy data from Study 1108 was presented at international oncology conferences (Rizvi et al 2015 ASCO). Overall, a low incidence of anti-drug antibody (ADA) has been observed. Of the 220 patients who received MEDI4736 monotherapy and for whom PK/ADA data were available as of July 2014, 5 were detected to be ADA positive, with an impact on PK/pharmacodynamics (PDx) reported in 1 patient.

Complete updated clinical data on MEDI4736 is found in the current IB.

1.1.4 Tremelimumab

Refer to the tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 5.5.3 for guidance on management of potential tremelimumab-related toxicities.

Tremelimumab, a CTLA-4 mAb of the IgG2 kappa isotype, is an IMT that is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. Tremelimumab is a human Ig G2 mAb directed against CTLA-4. CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T-cells upregulate CTLA-4, which binds to B7 ligands on antigen-presenting cells, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding

to B7, leading to prolongation and enhancement of T-cell activation and expansion. Thus, the mechanism of action of tremelimumab is indirect and is applied through enhancing T-cell-mediated immune response.

An extensive programme of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anti-cancer agents to support various cancer indications using different dose schedules. Tremelimumab has been administered as a single-agent treatment to patients participating in 11 sponsored clinical studies, 3 of which are ongoing. In total, more than 1400 patients with a variety of tumour types have been treated with tremelimumab given alone or in combination with other anti-cancer agents in 34 sponsored clinical studies.

Currently available data from the tremelimumab monotherapy clinical development programme suggests response rates that are more modest than the anti-PD-L1 approach, with a manageable but more pronounced toxicity profile in patients with a variety of solid malignancies, including patients with advanced NSCLC. Study A3671015, a Phase II, randomised, open-label trial examining tremelimumab 15 mg/kg every 90 days versus Best Supportive Care in advanced NSCLC patients who had completed first-line platinum-based chemotherapy, demonstrated PFS at 3 months of 10/44 in the tremelimumab arm (22.7%; 90% confidence interval [CI] 12.9%, 35.5%) and 5/42 in the Best Supportive Care arm (11.9%; 90% CI 4.8%, 23.4%). There were 3 patients who had a partial response (PR) in the tremelimumab arm, including 1 patient who had crossed over from the Best Supportive Care arm after progression of disease (PD), and there were no PR in the Best Supportive Care arm. Of note, all of these responding patients had squamous disease.

Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.4.2 of the protocol. Although the majority of the safety data for tremelimumab are based on mesothelioma and melanoma subject data, the mechanism of action for these risks is thought to be immune-mediated, reflective of the pharmacology of tremelimumab, and consistent with the safety profile of anti-CTLA-4 antibodies. Therefore, these safety risks are thought to be applicable to most subjects with solid tumours.

Complete updated clinical data including safety, efficacy and pharmacokinetic data can be found in the current version of the tremelimumab IB.

Emerging data from Study D4190C00006 in advanced NSCLC show that the combination of MEDI4736 and tremelimumab has a manageable safety profile (see Section 1.1.5).

1.1.5 MEDI4736 in combination with tremelimumab

1.1.5.1 Rationale for combination of anti-CTLA-4 and anti-PD-1/PD-L1

There are data suggesting that anti-tumour T-cells express multiple inhibitory receptors, a finding mirrored in murine models of chronic viral infections. The hypothesis for evaluating the combination of an anti-PD-L1 agent with an anti-CTLA-4 agent in the clinic is supported by pre-clinical data in mouse models of transplantable solid tumours that show superior

anti-tumour activity of combination therapy over monotherapy (Curran et al 2010, Mangsbo et al 2010). Pre-clinical data indicate that the mechanisms of activation of known sites for activity of CTLA-4 and PD-1 are non-redundant and therefore targeting both pathways may have additive or synergistic activity (Pardoll 2012).

In a relevant mouse model of melanoma, single blockade of either CTLA-4 or PD-1 enhanced the infiltration of activated T-cells into tumours, but the T-cells accumulated high levels of unblocked negative co-receptors that eventually limited their expansion. Blocking CTLA-4, PD-1 and PD-L1 simultaneously allowed T-cells to continue to survive and proliferate, and resulted in enhanced infiltration, activation and cytokine production, thereby reducing tumour-induced immune suppression and promoting tumour rejection (Drake 2012). In a study by Curran et al 2010, vaccination with irradiated B16 melanoma cells expressing the Flt3-ligand (Fvax) combined with antibody blockade of the negative T-cell co-stimulatory receptor CTLA-4 promoted rejection of pre-implanted tumours. However, despite CTLA-4 blockade, T-cell proliferation and cytokine production can be inhibited by the interaction of PD-1 with its ligands PD-L1 and PD-L2 or by the interaction of PD-L1 with B7-1. The study showed that the combination of CTLA-4 and PD-1 blockade was more than twice as effective as either agent alone in promoting the rejection of B16 melanomas in conjunction with Fvax (Curran et al 2010).

The concurrent administration of ipilimumab (anti-CTLA-4 mAb) and nivolumab (anti-PD-1 mAb) in the clinic was recently evaluated in a Phase I trial that demonstrated impressive preliminary evidence of improved benefit in advanced melanoma patients. The overall response rate (modified World Health Organisation [WHO] criteria) was 53% at the MTD, including 3 patients with a complete response (CR), and all responding patients experienced a ≥80% decline in tumour burden at 12 weeks. Across all dose levels in this dose-escalation study, the response rate was 40%. The response seen appeared to be both rapid and deep. Also, responses to the combined therapy were generally durable and were observed even in patients whose treatment was terminated early because of AEs (Wolchok et al 2013).

The combination was tolerated, but there were more Grade 3 or 4 events compared to historical data on either agent when given alone. These events were manageable. Grade 3 or 4 AEs related to therapy occurred in 53% of patients. The events reported were qualitatively similar to previous experience with monotherapy as immune events and were generally reversible (Wolchok et al 2013). Improving the safety profile of such combinations, however, will be important.

Preliminary data from a Phase I study of ipilimumab and nivolumab in first-line NSCLC showed an ORR of 11 to 33% and a PFS rate at 24 weeks of 20 to 51% across different histologies and looking at different dose combinations of the 2 agents (Antonia et al 2014 ASCO).

In conclusion, the pre-clinical and clinical research suggests that combinations of immunotherapy agents may generate superior anti-tumour activity compared to single agent immunotherapy, which may translate into higher and more durable rates of response.

Therefore, concurrent targeting of immunologic checkpoints with multiple inhibitory/stimulatory molecules may enhance efficacy.

1.1.5.2 Study D4190C00006 Phase Ib experience

Study D4190C00006 is an ongoing Phase Ib dose-escalation and dose-expansion study of MEDI4736 in combination with tremelimumab in patients with advanced NSCLC. Patients with histologically- or cytologically-confirmed locally advanced or metastatic NSCLC, with at least 1 measurable lesion, with adequate organ and marrow function, and with Eastern Cooperative Oncology Group performance status of 0-1, are eligible. Patients cannot have had more than 3 prior lines of therapy in the metastatic setting including standard of care.

Two dosing schedules are being evaluated in this study: a once every 4 weeks (Q4W) schedule (MEDI4736 Q4W up to Week 48 plus tremelimumab Q4W up to Week 24 then once every 12 weeks [Q12W] until Week 48) and an alternative Q2W schedule for 18 doses or until Week 36.

The first patient in Cohort 1a was dosed in October 2013. As of 27 January 2015, a total of 74 patients have been treated in the study with a minimum of 3 patients in each cohort as detailed in Table 1.

Table 1 Cohorts in Study D4190C00006

Cohort	MEDI4736	Tremelimumab	Patients Treated
	Q4W Dosing Schedule		
1a	3 mg/kg	1 mg/kg	3
2a	10 mg/kg	1 mg/kg	3
3a	15 mg/kg	1 mg/kg	12
3b	10 mg/kg	3 mg/kg	3
4	20 mg/kg	1 mg/kg	11
4a	15 mg/kg	3 mg/kg	11
5	15 mg/kg	10 mg/kg	9
5a	20 mg/kg	3 mg/kg	6
Q4W Total			58
	Q2W Dosing Schedule		
8	10 mg/kg	1 mg/kg	6
9	10 mg/kg	3 mg/kg	10
Q2W Total			16
Overall Total			74

Patients have received between 1 and 9 doses of tremelimumab and between 1 and 13 doses of MEDI4736.

1.1.5.3 Safety and efficacy on the overall Study D4190C00006

As of the 27 January 2015 cut-off date, 2 patients out of 6 treated in the Q4W MEDI4736 20 mg/kg and tremelimumab 3 mg/kg (M20/T3; Cohort 5a) experienced a DLT. The DLTs were: (1) increased AST (Grade 3) on Day 29 of Cycle 1 and (2) increased amylase (Grade 3) and increased lipase (Grade 4) occurring on Day 9 of Cycle 1. Adverse events regardless of causality were reported in 62 of the 74 patients (83.8%) across all dose cohorts. Adverse events were considered related to treatment in 50 patients (67.6%). Twenty-four of these events were Grade 1 or Grade 2, with Grade ≥3 events reported in 26 patients (35.1% of total population). No consistent pattern in the nature, frequency, or severity of AEs has been noted with escalating doses of the combination.

With the exception of the 20 mg/kg MEDI4736 and 1 mg/kg tremelimumab (M20/T1) cohort, all patients within each Q4W cohort had at least 1 AE (Table 2). Across the Q4W dose cohorts in which tremelimumab was administered at 1 mg/kg, rates of treatment related AEs, Grade 3 and 4 AEs, and SAEs were least frequent in the M3/T1 cohort. Grade 3 treatment-related AEs and were highest in the M20/T3 cohort.

Table 2 Rate Summary of All Adverse Events in the Q4W Cohorts, As-treated Population, Study D4190C00006

Adverse Event Outcome (MedDRA V 17.1)	M3/T1 (N = 3) n (%)	M10/T1 (N = 3) n (%)	M15/T1 (N = 12) n (%)	M10/T3 (N = 3) n (%)	M20/T1 (N = 11) n (%)	M15/T3 (N = 11) n (%)	M15/T10 (N = 9) n (%)	M20/T3 (N = 6) n (%)	Total (N = 58) n (%)
1 or more event	3 (100)	3 (100)	12 (100)	3 (100)	7 (63.6)	11 (100)	9 (100)	6 (100)	54 (93.1)
1 or more Grade 3 event	0	2 (66.7)	9 (75.0)	3 (100)	3 (27.3)	5 (45.5)	7 (77.8)	6 (100)	35 (60.3)
1 or more Grade 4 event	0	1 (33.3)	1 (8.3)	1 (33.3)	1 (9.1)	0	0	1 (16.7)	5 (8.6)
1 or more serious event	1 (33.3)	2 (66.7)	7 (58.3)	2 (66.7)	2 (18.2)	7 (63.6)	7 (77.8)	6 (100)	34 (58.6)
1 or more event leading to discontinuation of study drug	1 (33.3)	1 (33.3)	2 (16.7)	2 (66.7)	0	5 (45.5)	3 (33.3)	5 (83.3)	19 (32.8)
Death	0	1 (33.3)	1 (8.3)	0	0	2 (18.2)	0	2 (33.3)	6 (10.3)
1 or more related event	1 (33.3)	3 (100)	7 (58.3)	3 (100)	7 (63.6)	9 (81.8)	8 (88.9)	5 (83.3)	43 (74.1)
1 or more ≥Grade 3 related event	0	2 (66.7)	5 (41.7)	2 (66.7)	2 (18.2)	4 (36.4)	4 (44.4)	5 (83.3)	24 (41.4)
1 or more related serious event	0	1 (33.3)	3 (25.0)	2 (66.7)	2 (18.2)	5 (45.5)	4 (44.4)	5 (83.3)	22 (37.9)
1 or more related event leading to discontinuation of study drug	0	1 (33.3)	1 (8.3)	2 (66.7)	0	4 (36.4)	3 (33.3)	4 (66.7)	15 (25.9)
Death related to study drug	0	1 (33.3)	0	0	0	0	0	1 (16.7)	2 (3.4)

MedDRA Medical Dictionary for Regulatory Activities; M(x)/T(y) MEDI4736 (x) mg/kg and tremelimumab (y) mg/kg; Q4W every 4 weeks.

Overall, 62 (83.8%) of the 74 patients reported an AE regardless of causality. The most frequently (10 or more patients) reported AEs were fatigue (37.8%; 28 patients); diarrhoea (32.4%; 24 patients); amylase increased and pruritus (16.2%; 12 patients); decreased appetite, dyspnoea, nausea and rash (14.9%; 11 patients each), and headache and pyrexia (13.5%; 10 patients).

Twenty of the 62 patients who experienced AEs regardless of causality had events that were Grade 1 or 2 in severity. Forty-two of the 62 patients reported ≥Grade 3 events. The most frequently reported ≥Grade 3 events (in 3 or more patients) were diarrhoea (7 patients); colitis (6 patients); increased lipase (4 patients); and anaemia, increased ALT, increased AST, dehydration and pneumonitis (3 patients each).

Fifty of the 74 patients reported a treatment-related AE. The most frequently reported treatment-related AEs were fatigue (24.3%; 18 patients); diarrhoea (21.6%; 16 patients); increased ALT (13.5%, 10 patients); pruritus (12.2%; 9 patients); and rash (10.8%; 8 patients). Twenty-four of the 50 patients who experienced treatment-related AEs reported Grade 1 or 2 events only. Twenty-six of the 50 patients reported ≥Grade 3 events. The most frequently reported treatment-related ≥Grade 3 events (in 3 or more patients) were colitis and diarrhoea (6 patients each), increased lipase (4 patients), and increased ALT, increased AST and pneumonitis (3 patients each).

Within the total study population, 21 patients (28.4%) discontinued treatment due to AEs. The most frequent AEs (more than 1 patient) leading to treatment discontinuation were colitis (5 patients); pneumonitis (4 patients); diarrhoea (3 patients); and increased AST and dyspnoea (2 patients each). The episodes of colitis, diarrhoea, increased AST, and pneumonitis were all considered to be treatment related. The percentage of patients with AEs leading to discontinuation was highest in the M20/T3 cohort (83.3%, 5/6).

Eleven patients (14.9%) have died, of which 9 were due to disease and 2 to treatment-related toxicities (Grade 5 polymyositis and Grade 5 neuromuscular disorder [verbatim term]). Ten of the 11 patients died within 90 days after the last dose.

In Study D4190C00006, PK (n=55), ADA (n=60), and soluble PD-L1 (sPD-L1; n=69) data were collected from 10 cohorts following Q4W or Q2W regimens. An approximately dose-proportional increase in PK exposure (maximum plasma concentration [C_{max}] and area under the plasma drug concentration-time curve from time zero to Day 28 post-dose [$AUC_{0\text{-}28day}$]) 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. The observed PK exposures of MEDI4736 and tremelimumab following combination were in line with respective monotherapy data, indicating no PK interaction between these 2 agents.

Four of 60 patients (2 at 15 mg/kg MEDI4736 Q4W plus 10 mg/kg tremelimumab Q4W, 1 each at 15 mg/kg MEDI4736 Q4W plus 1 mg/kg tremelimumab Q4W and 10 mg/kg MEDI4736 Q4W plus 3 mg/kg tremelimumab Q4W) were ADA positive for either anti-MEDI4736 or anti-tremelimumab antibodies post-treatment. MEDI4736 PK was

impacted in only 2 of 4 patients following 15 mg/kg MEDI4736 Q4W plus 1 mg/kg tremelimumab Q4W and 15 mg/kg MEDI4736 Q4W plus 10 mg/kg tremelimumab Q4W. One of 53 patients (15 mg/kg MEDI4736 Q4W plus 1 mg/kg tremelimumab Q4W) was ADA positive with no impact on PK.

Following MEDI4736 in combination with tremelimumab, complete sPD-L1 suppression (surrogate for PD-L1 targeting) was observed in almost all patients over the dose range of 3 to 20 mg/kg MEDI4736 Q4W or Q2W. In 2 patients (1 patient each at 10 mg/kg MEDI4736 Q4W plus 1 mg/kg tremelimumab Q4W and 15 mg/kg MEDI4736 Q4W plus 1 mg/kg tremelimumab Q4W), showed partial sPD-L1 suppression at some visits followed by complete suppression after repeated dosing. One patient following 15 mg/kg MEDI4736 Q4W plus 10 mg/kg tremelimumab Q4W showed partial suppression on Day 29 and was ADA positive with an impact on PK. No clear dose-dependent changes in sPD-L1 were identified over the dose range of 3 to 20 mg/kg MEDI4736 Q4W or Q2W.

As of the 27 January 2015 cut-off date, a total of 53 of 74 patients were evaluable for efficacy with at least 8-weeks of follow-up. Of these, there were 12 patients (23%) with PR, 14 patients (26%) with stable disease (SD), and 19 patients (36%) with progressive disease (PD) as assessed by RECIST guidelines v1.1 (Eisenhauer et al 2009).

Other active combination studies of MEDI4736 and tremelimumab include
Study LUD2013-003, which is an open-label, dose-escalation, and dose-expansion study in adults with advanced solid tumours (3 patients were enrolled as of 18 February 2014, with no safety data yet available as of this cut-off date).

Updated information on the safety and efficacy profile of MEDI4736+tremelimumab combination therapy are provided in the current MEDI4736 and tremelimumab IBs.

1.1.5.4 Safety and efficacy of dose of the combination of MEDI4736 20 mg/kg Q4W and tremelimumab 1 mg/kg Q4W

As of the 27 January 2015 cut-off date, in Study D4190C00006, in the 20 mg/kg MEDI4736 and 1 mg/kg tremelimumab cohort, 11 patients have received 1 to 5 doses of tremelimumab and MEDI4736. Seven patients (63.6%) reported at least 1 AE. Adverse events reported by more than 1 patient were fatigue (4 patients) and diarrhoea, blood thyroid stimulating hormone increased, decreased appetite, and dizziness (2 patients each). All 7 of these patients reported at least 1 treatment-related AE, with each event reported by 1 patient each.

Three patients (27.3%) experienced Grade 3 or higher AEs regardless of causality. These events were sepsis, ALT increased, AST increased, blood potassium decreased, haemoglobin decreased, lipase increased, platelet count decreased, and sciatica (1 patient each). Two of the 3 patients experienced Grade 3 or higher AEs that were treatment-related. These AEs were sepsis, ALT increased, AST increased, lipase increased, and platelet count decreased (1 patient each).

Two patients (18.2%) experienced a total of 6 SAEs (colitis, sepsis, increased ALT, increased AST, decreased platelet count, and depressed level of consciousness).

There were no AEs leading to treatment discontinuation. No patient in this cohort died due to an AE.

A total of 5 of 11 patients were evaluable for efficacy as of the 27 January 2015 cut-off date, 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 progressive disease (PD). (Note: One of the 5 patients initially deemed to be evaluable was subsequently determined to have had a scan outside of the analysis window; efficacy results for this patient were not available at the time of data cut-off [DCO].) Updated safety and efficacy data from D4190C00006 was presented at international oncology conferences (Antonia et al 2015 ASCO, Rizvi et al 2015 SITC).

Overall, the safety profile of 20 mg/kg MEDI4736 in combination with 1 mg/kg tremelimumab continues to be manageable and supports further development of the combination at this dose (see Dosing Modification and Toxicity Management Guidelines in Section 5.5.3).

1.1.6 Genetic data

The pharmacogenetic (PGx) research elements of this study (relating to deoxyribonucleic acic [DNA]) are optional. Refer to Appendix D.

1.2 Research hypothesis

The research hypothesis for this study is to determine whether:

- MEDI4736 10 mg/kg (Q2W via iv infusion for up to 12 months) shows improved efficacy in terms of OS and PFS compared with Standard of Care in the treatment of patients with locally advanced or metastatic PD L1–positive (where positive is defined as ≥25% of tumour cells with membrane staining [proprietary PD-L1 immunohistochemistry assay; Ventana Medical Systems, Inc]), NSCLC (Stage IIIB-IV), who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen for NSCLC.

- MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg (Q4W iv for up to 12 weeks) then MEDI4736 10 mg/kg (Q2W iv for up to 34 weeks) shows improved efficacy in terms of OS and PFS compared with Standard of Care in the treatment of patients with locally advanced or metastatic PD L1–negative (ie, those with <25% of tumour cells with membrane staining) NSCLC (Stage IIIB-IV), who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen for NSCLC.

This will be assessed via the primary objective of this study, which is to assess the efficacy, in terms of OS and PFS, of MEDI4736 versus Standard of Care in the PD-L1-positive patient

population or MEDI4736 plus tremelimumab (MEDI4736+tremelimumab) compared with Standard of Care in the PD-L1-negative patient population.

Secondary efficacy objectives for both sub-studies include evaluation of the proportion of patients alive at 12 months from randomisation (OS12), ORR, duration of response (DoR), the proportion of patients alive and progression free at 6 months from randomisation (APF6) and the proportion of patients alive and progression free at 12 months from randomisation (APF12), and the time from randomisation to second progression (PFS2). Other secondary objectives for both sub-studies include an assessment of safety and tolerability, MEDI4736 and tremelimumab PK exposure, immunogenicity, and patient reported outcomes (PRO). Exploratory objectives are also included. Additionally Sub-study B will investigate whether MEDI4736+tremeliminab is superior to each of its constituent components through separate comparisons with MEDI4736 monotherapy and tremelimumab monotherapy. If appropriate, and depending upon the results and timing of the contribution of components analysis, there is scope for the same comparisons to be repeated at the time of final analysis across further efficacy endpoints as well as comparisons with the Standard of Care therapy.

Section 12.3 provides information on how the sample size for the study was determined.

1.3 Rationale for conducting this study

Current therapies for advanced NSCLC have poor outcomes (low 5-year survival [11%], poor response to systemic treatment for patients with refractory advanced NSCLC [<10%], with median survival of approximately 6 months) (D'Addario et al 2010, GLOBOCAN 2008, Hanna et al 2004). There is still a significant unmet medical need for additional treatment options for use in this patient population (see Section 1.1.1).

Although clinical experience with MEDI4736 alone, tremelimumab alone and with the combination of MEDI4736 plus tremelimumab is limited, currently available data from the MEDI4736 monotherapy clinical development programme indicates encouraging response rates and DoR, with a manageable safety profile in patients with a variety of solid malignancies, including patients with advanced NSCLC. Data on MEDI4736 monotherapy presented at ESMO 2014 showed an ORR of 16% in the overall NSCLC patient population and a 25% ORR in the PD-L1-positive subset of patients (Antonia et al 2014 ESMO). More recent data has been presented at international oncology conferences (Rizvi et al 2015 ASCO). Please refer to latest MEDI4736 IB for complete details of efficacy of MEDI4736 across all clinical programs.

Currently available data from the tremelimumab monotherapy clinical development programme suggests response rates that are more modest than the anti-PD-L1 approach, with a manageable but more pronounced toxicity profile in patients with a variety of solid malignancies, including patients with advanced NSCLC. Study A3671015, a Phase II, randomised, open-label trial examining tremelimumab 15 mg/kg every 90 days versus Best Supportive Care in advanced NSCLC patients who had completed first-line platinum-based chemotherapy, demonstrated PFS at 3 months of 10/44 in the tremelimumab arm (22.7%; 90% CI 12.9%, 35.5%) and 6/42 in the Best Supportive Care arm (11.9%; 90% CI 6.4%, 26.3%).

There were 3 patients who had a PR in the tremelimumab arm, including 1 patient who had crossed over from the Best Supportive Care arm after PD, and there were 0 PR in the Best Supportive Care arm. Of note, all of these responding patients had squamous disease. As discussed in Section 1.1.5.1, non-clinical and clinical research suggests that combinations of IMT agents may generate superior anti-tumour activity, compared to single-agent immunotherapy, which may translate into higher and more durable rates of response. As a result, concurrent targeting of immunologic checkpoints with multiple inhibitory/stimulatory molecules may enhance efficacy. Early data from Study D4190C00006 (MEDI4736 in combination with tremelimumab) has shown an acceptable and manageable safety profile, including at the proposed dose for this study of 20 mg/kg MEDI4736 and 1 mg/kg tremelimumab. Efficacy data are limited but there are early signs of clinical activity in an advanced/metastatic NSCLC patient population. Published data from a combination of other PD-1 and CTLA-4 inhibitors have demonstrated impressive preliminary evidence of improved benefit in melanoma patients, with a response rate of 53% at the MTD; all responding patients experienced a ≥80% decline in tumour burden at 12 weeks. Preliminary data from a Phase I study of ipilimumab and nivolumab in first-line NSCLC showed an ORR of 11 to 33% and a PFS rate at 24 weeks of 20 to 51% across different histologies and looking at different dose combinations of the 2 agents (Antonia et al 2014 ASCO).

Current experience from studies with single-agent IMTs that target the PD-1/PD-L1 pathway suggest that clinical responses may be enhanced in a subset of patients 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 anti-PD-1/PD-L1 agents. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumour cells and or tumour-infiltrating cells may be associated with greater clinical benefit. For example, data presented by Roche at the Annual Meeting of the ASCO 2013 (Powderly et al 2013) suggested that PD-L1 expression on infiltrating lymphocytes in NSCLC, melanoma and renal cell carcinoma patient cohorts is associated with greater clinical benefit from anti-PD-L1 treatment. Using a proprietary assay for PD-L1 immunohistochemistry, a 36% ORR was observed in patients who had PD-L1–positive tumours, with 50% of patients with PD-L1–positive tumours having SD and 33% having PRs. Similarly, in data presented at the Annual Meeting of the ASCO 2013 by Bristol-Myers Squibb (Grosso et al 2013), PD-L1 staining, when assessed using a different method and scoring algorithm, appeared to be associated with greater clinical benefit in patients treated with nivolumab (anti-PD-1). A 44% ORR was observed in patients with PD-L1-positive tumours versus a 17% ORR in patients with PD-L1-negative tumours. Additionally, patients with tumours that were PD-L1 positive had a higher PFS (9.1 versus 2.0 months) and OS than patients with PD-L1-negative tumours (21 versus 12 months).

Also, in a data set presented by Merck & Co at the World Conference on Lung Cancer (Garon et al 2013), analysis of the relationship between PD-L1 expression status and response rates in a cohort of patients with NSCLC indicated that tumour samples displaying high levels of PD-L1 expression (according to their assay criteria) were associated with response rates of 67% (6/9; per irRC) and 57% (4/7; per RECIST 1.1). In contrast, tumour samples expressing

zero/low levels of PD-L1 were associated with response rates of 4% (1/24; per irRC) and 9% (2/22; per RECIST 1.1).

Data on MEDI4736 presented at ESMO 2014 showed an ORR of 16% in the overall NSCLC patient population and a 25% ORR in the PD-L1-positive subset of patients (Antonia et al 2014 ESMO). More recent data has been presented at international oncology conferences (Rizvi et al 2015 ASCO). Therefore, it appears that the selection of patients based on PD-L1 expression within the tumour microenvironment may improve the probability and/or quality of responses to PD-1 pathway-targeting agents and, therefore, may have merit as a patient enrichment tool.

Based on this information, the likelihood of response to MEDI4736 monotherapy is expected to be higher in patients with PD-L1-positive tumours.

While the Ventana PD-L1 assay is expected to successfully select NSCLC patients with PD-L1-positive tumour for response with MEDI4736 monotherapy, a few NSCLC patients with PD-L1-negative tumours have been noted to achieve a response with MEDI4736 in the FTIH study (Antonia et al 2014 ESMO). This is not surprising as PD-L1, as a biomarker, has limitations due to its dynamic and heterogeneous nature. Therefore, until a more selective biomarker is identified, and considering the heavy toxicity burden of Standard of Care and the MEDI4736 AE profile, MEDI4736 monotherapy in NSCLC patients with PD-L1-negative tumours should be explored.

Separately, it has been noted earlier that a Phase II study examining tremelimumab in advanced NSCLC patients produced a trend toward improved PFS at 3 months and a 4.8% PR rate. The more intensive tremelimumab treatment regimen of 10 mg/kg Q4W has not been examined as monotherapy in NSCLC. Tremelimumab at a concentration of 30 μg/mL enhanced IL-2 release (in vitro) and showed anti-tumour activity (in vivo), and was consequently identified as the target concentration. As a result, PK simulations indicate that at a dose of 10 mg/kg Q4W for 6 months, approximately 90% of patients are expected to be above this target level of 30 μg/mL during the induction phase. An enhanced AUC at this dose may offer greater exposure which may confer benefit beyond what was noted in Study A3671015. Therefore, this study will explore tremelimumab monotherapy at a dose of 10 mg/kg Q4W for 24 weeks followed by 10mg/kg Q12W up to an additional 24 weeks.

Expression of PD-L1 may have less bearing when a combination of checkpoint inhibitors is utilised. A study investigating the combination of a PD-1 inhibitor (nivolumab) and a CTLA-4 inhibitor (ipilimumab) in patients with melanoma suggested that the combination of CTLA-4 and PD-1 blockade may be active regardless of tumoural PD-L1 expression (Wolchok et al 2013). Early data from Study D4190C00006 (combination of MEDI4736 plus tremelimumab) has shown consistent clinical activity in an advanced/metastatic NSCLC patient population. The combination of 2 immune checkpoint mAb inhibitors is likely to increase the frequency and/or severity of some toxicities, such as immune-mediated toxicities. Emerging safety data from these early phase combination studies suggests this to be the case.

Examination of the combination of MEDI4736 plus tremelimumab is important to clearly define the activity and safety profile compared to Standard of Care.

Therefore, NSCLC patients with PD-L1-negative tumours are a subset of patients with limited therapeutic options with a high unmet need, who may have a greater signal of activity from the combination of MEDI4736 plus tremelimumab versus MEDI4736 monotherapy or tremelimumab monotherapy. As the toxicity profile varies amongst these therapies, exploration of the combination of MEDI4736 plus tremelimumab versus either of the constituent components as monotherapy agents is an important study that will clearly establish the proper risk benefit for each therapy.

1.4 Benefit/risk and ethical assessment

Refer to the current IBs for information on the potential benefits of MEDI4736 and tremelimumab and an assessment of the potential and known risks.

Lung cancer is an aggressive, heterogeneous, and complex disease that is often detected at an advanced stage, with no curative option for the majority of patients. Despite advances in the diagnosis, imaging, staging and treatment of NSCLC, the estimated overall 5-year survival for patients in Europe continues to be low (11%) and the outlook for those with refractory advanced NSCLC is extremely poor (D'Addario et al 2010, GLOBOCAN 2008, Hanna et al 2004). Common third-line treatment for NSCLC in major global markets includes: vinorelbine, TKIs and gemcitabine (Decisions Resources 2013). For these patients, clinical trials, experimental treatment, or best supportive care are among the considered treatment options (Azzoli et al 2009, Syrigos et al 2011).

1.4.1 MEDI4736 monotherapy: Sub-study A

MEDI4736 has been given to humans as part of ongoing studies where it is given either as a single drug or in combination with other drugs. The majority of the safety data currently available for MEDI4736 is based on the FTIH, single agent study 1108 in patients with advanced solid tumours. As of 14 July 2014, a total of 414 patients have entered into this study, of which 393 had received MEDI4736 at 10 mg/kg Q2W. The most frequently reported (≥10% of patients) treatment-emergent AEs (all grades) were fatigue, dyspnoea, nausea, constipation and decreased appetite. The majority of these treatment-emergent AEs were Grades 1 to 2 in severity and manageable by the general treatment guidelines as described in the current MEDI4736 study protocols. Treatment-related AEs were reported for 162 of 393 patients (41.2%). The most frequently reported (≥2% of patients) treatment-related AEs (all grades) were fatigue (13.5%); nausea (8.4%); diarrhoea, decreased appetite, and rash (5.3% each); vomiting (4.8%); pruritus (4.1%); dyspnoea (3.8%); pyrexia (3.1%); hypothyroidism (2.8%); increased ALT, increased AST, and cough (2.5% each); myalgia (2.3%); and abdominal pain and dizziness (2.0% each). No DLTs have been reported.

Data presented at ESMO 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; drug-related AEs leading to discontinuation reported in 1% of patients; no drug-related colitis or hyperglycaemia of any grade and no Grade ≥3 pneumonitis were reported and no drug-related AEs leading to death were reported (Antonia et al 2014 ESMO). More recent data has been presented at international oncology conferences (Rizvi et al 2015 ASCO). For further details on the safety data on MEDI4736, please refer to the current IB.

Potential risks based on the mechanism of action of MEDI4736 and related molecules include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity, endocrinopathy, pneumonitis and neuropathy. As with the administration of any foreign protein and/or other biologic agents, other important potential risks include anaphylaxis/anaphylactoid/ hypersensitivity reactions, serious infections, infusion reactions, immune-complex disease and the development of ADAs. Anti-drug antibodies could result in immune-complex disease with manifestations such as arthralgias, serum sickness, and vasculitis and/or could result in altered MEDI4736 levels or activity.

Among the most frequent treatment-related AEs noted with other mAbs targeting the PD-1/PD-L1 pathway are fatigue, rash, diarrhoea and pruritus. Reported immune-mediated AEs of ≥Grade 3 include pneumonitis, diarrhoea, ALT increased and AST increased.

Promising evidence of clinical activity has been observed for molecules similar to MEDI4736, including other mAbs targeting the PD-1/PD-L1 pathway. In these studies, encouraging response rates and durable responses have been observed across a range of tumour types (Berger et al 2008, Brahmer et al 2010, Gordon et al 2013, Robert et al 2011, Topalian et al 2012).

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

Of the 184 patients with NSCLC treated with MEDI4736 (all dose levels), 49 patients were evaluable for response analysis. Seven patients (14.3%) had a best overall response of CR/PR (confirmed and unconfirmed). The DCR was 36.7% (18 of 49 patients). Programmed cell death ligand 1 status (based on Ventana assay) was known for 26 of the 49 evaluable patients (the 26 patients were treated with MEDI4736 10 mg/kg Q2W), of whom 8 were PD-L1 positive. A best overall response of CR/PR (confirmed and unconfirmed) was reported in 3 of 8 (37.5%) PD-L1-positive patients and in 1 of 18 (5.6%) PD L1-negative patients.

Efficacy data on the NSCLC patients in Study 1108, presented at ESMO 2014 (cut-off date of 21 August 2014), showed a disease control rate 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 in patients with PD-L1 positive (≥25% of tumour cells with membrane staining for PD-L1) tumours (25%; 12 CR/PR; n=48) compared to patients with PD-L1 negative tumours (10%; 7 CR/PR; n=74) (Antonia et al 2014 ESMO). More recent data has been presented at international oncology conferences (Rizvi et al 2015 ASCO). Please refer to latest MEDI4736 IB for complete details of efficacy of MEDI4736 across all clinical programs.

As discussed in Section 1.3, current experience from studies with single-agent IMTs that target the PD-1/PD-L1 pathway suggest that clinical responses may be enhanced in 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. Data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumour cells and or tumour-infiltrating cells may be associated with greater clinical benefit. It appears that the selection of patients based on PD-L1 expression within the tumour microenvironment may improve the probability and/or quality of responses to PD-1 pathway-targeting agents and, therefore, may have merit as a patient enrichment tool.

Based on this information, the likelihood of response to MEDI4736 monotherapy is expected to be higher in NSCLC patients with PD-L1-positive tumours; nonetheless, responses were also noted in a few NSCLC patients with PD-L1-negative tumours.

In view of the potential for MEDI4736 to have anti-tumour activity in the NSCLC patient population with PD-L1-positive and negative tumours, the risk-benefit assessment favours the proposed enrolment of patients with PD-L1 positive tumours into Sub-study A, MEDI4736 monotherapy versus Standard of Care, and patients with PD-L1-negative tumours into Sub-Study B, MEDI4736+tremelimumab in combination versus Standard of Care (see Section 1.4.2).

1.4.2 MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736 plus tremelimumab: Sub-study B

The benefits and risks of MEDI4736 given as a monotherapy agent are discussed in Section 1.4.1.

Tremelimumab has been administered as a single-agent treatment to patients participating in 11 sponsored clinical studies, 3 of which are ongoing. In total, more than 1400 patients with a variety of tumour types have been treated with tremelimumab given alone or in combination with other anti-cancer agents in 34 sponsored clinical studies.

Risks with tremelimumab monotherapy are gastrointestinal 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; other gastrointestinal events (ulcerative colitis, dehydration, nausea and

vomiting); hepatic events (hepatitis and liver enzyme elevations); pneumonitis and interstitial lung disease; clinical manifestations of pancreatitis; nervous system events (encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness); cytopenias (thrombocytopenia, anemia and neutropenia); infusion-related reactions, anaphylaxis and allergic reactions; renal events (renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalaemia); autoimmune diseases (autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis); hyperglycaemia and diabetes mellitus; and pyrexia.

Further information on the identified and potential risks can be found in the current version of the tremelimumab IB.

Using pooled data from monotherapy clinical studies, AEs (all grades) reported very commonly (≥10% of patients) were diarrhoea, 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.

The majority of the updated reference safety information for tremelimumab is based on data from the mesothelioma (Study D4880C00003 [DETERMINE]) and melanoma (legacy data from tremelimumab mesothelioma/melanoma multiple dose pools) subject data, but is consistent with the safety profile of anti-CTLA-4 antibodies and expected to be applicable to most subjects with solid tumours. A detailed summary of these studies and the tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

Although clinical experience with the single agent, tremelimumab, in NSCLC is limited, a Phase II study (A3671015) examining tremelimumab (15 mg/kg every 90 days) as maintenance treatment post-platinum doublet chemotherapy in advanced NSCLC patients produced a trend toward improved PFS at 3 months and a 4.8% PR rate. The more intensive tremelimumab treatment regimen of 10 mg/kg Q4W has not been examined as monotherapy in NSCLC. In this study (Study D4191C00004), tremelimumab will be given at a dose of 10 mg/kg Q4W for 24 weeks and then 10 mg/kg Q12W for up to a further 24 weeks. The enhanced AUC offered by this greater exposure may confer benefit beyond what was seen in the previous Phase II study.

As discussed in Section 1.1.5, data from the dose-escalation combination study of MEDI4736 plus tremelimumab in NSCLC patients have shown an acceptable and manageable safety profile in an advanced/metastatic NSCLC patient population, and signs of clinical activity have been seen. As of 27 January 2015, 53 patients have at least 8 weeks of follow-up data. Twelve patients had best overall responses of PR and 14 patients had SD as assessed by RECIST.

As of 27 January 2015, AEs regardless of causality were reported in 62 of the 74 patients (83.8%) across all dose cohorts. Adverse events were considered related to treatment in

50 patients (67.6%). Twenty-four of the 50 patients who experienced treatment-related AEs reported Grade 1 or 2 events only. Twenty-six of the 50 patients reported ≥Grade 3 events.

Data in the literature from combinations of the same class of drugs showed higher response rates than those obtained with single-agent therapy, and these responses appeared to be rapid and deep. Also, responses to combined therapy were generally durable and were observed even in patients whose treatment was terminated early because of AEs (Wolchok et al 2013).

Also, as previously discussed in Section 1.3, the selection of patients based on PD-L1 expression within the tumour microenvironment may improve the likelihood of response to MEDI4736 monotherapy in patients with PD-L1-positive tumours; however, patients with PD-L1-negative tumours also showed clinical benefit.

In Study A3671015, patients with advanced NSCLC given tremelimumab had limited benefit and a trend toward improved PFS at 3 months. The approach of using 10 mg/kg Q4W to enhance AUC merits testing on a larger scale as monotherapy.

Expression of PD-L1 may have less bearing when a combination of checkpoint inhibitors is utilised. A study investigating the combination of a PD-1 inhibitor (nivolumab) and a CTLA-4 inhibitor (ipilimumab) in patients with melanoma suggested that the combination of CTLA-4 and PD-1 blockade may be active regardless of tumoural PD-L1 expression (Wolchok et al 2013).

With the proliferation of agents targeting the NSCLC patients with PD-L1 positive tumours, the NSCLC patients with PD-L1–negative tumours represent an unmet medical need with limited therapeutic options and it is imperative that different monotherapeutic and combinatorial approaches be examined. It is also of importance to assess the efficacy of the combination versus each of its separate components when administered as monotherapy agents.

Emerging safety data from these early studies exploring the combination of immune checkpoint inhibitors indicate an increased frequency and/or severity of some toxicities, such as immune-related toxicities; which are manageable based on immune-related toxicity management guidelines.

Therefore, Sub-study B offers NSCLC patients with PD-L1-negative expressing tumours acceptable therapeutic options with manageable safety profiles.

1.4.3 Summary of potential benefits and risks of other immunotherapy agents

Other mAbs targeting the PD-1/PD-L1 pathway are currently in clinical development. Among the most frequent treatment-related AEs noted with these antibodies are fatigue, rash, diarrhoea and pruritus. Immune-mediated AEs of ≥Grade 3 reported include pneumonitis, diarrhoea, ALT increased and AST increased.

Other relevant risks include those associated with biological and immunotherapy agents. Ipilimumab and tremelimumab are both immunomodulatory antibodies that target CTLA-4 and have been studied extensively across multiple tumour types. Ipilimumab is marketed for the treatment of metastatic or unresectable melanoma based on improvements in OS as a single agent and in combination with chemotherapy. Immune-mediated AEs of Grade 3 or higher observed during Phase III studies of ipilimumab occurred in 15% of patients and included enterocolitis (7%), hepatitis (2%), dermatitis (2.5%) and endocrinopathy (1.8%) (YERVOY™ prescribing information). Adverse events similar to those reported with ipilimumab were observed during the clinical development of tremelimumab in melanoma, with diarrhoea (40%), pruritus (23%), rash (22%), nausea (22%) and fatigue (17%) being the most common (Kirkwood et al 2010). Grade 3 or higher AEs observed were diarrhoea (11%), fatigue (2%), rash (1%), nausea (1%), vomiting (1%) and anorexia (1%).

Promising evidence of clinical activity has been observed for molecules similar to tremelimumab and MEDI4736, including other mAbs targeting the CTLA-4 and PD-1/PD-L1 pathways, respectively. In these studies, encouraging response rates and durable responses have been observed across a range of tumour types (Berger et al 2008, Brahmer et al 2010, Gordon et al 2013, Robert et al 2011, Topalian et al 2012, YERVOY™ prescribing information, OPDIVO® prescribing information, KEYTRUDA® prescribing information).

1.4.4 Summary benefit: risk statement

Lung cancer is an aggressive, heterogeneous, and complex disease that is often detected at an advanced stage, with no curative option for the majority of patients. Despite advances in the diagnosis, imaging, staging and treatment of NSCLC, the estimated overall 5-year survival for patients in Europe continues to be low (11%) and the outlook for those with refractory advanced NSCLC is extremely poor (D'Addario et al 2010, Hanna et al 2004). There remains a significant unmet medical need for additional treatment options for NSCLC patients, especially in the third-line or greater setting where treatment options are limited.

Emerging clinical data show that MEDI4736 has an acceptable and manageable safety profile, and the potential for MEDI4736 to have anti-tumour activity in the NSCLC population with PD-L1-positive tumours supports a risk-benefit assessment that favours the proposed enrolment of such patients into MEDI4736 monotherapy in Sub-study A of this study.

In NSCLC patients with PD-L1-negative tumours, MEDI4736 monotherapy is expected to confer limited efficacy with a manageable safety profile consistent with the FTIH study (Study 1108; see Section 1.1.3). Emerging data from the tremelimumab clinical development

programme suggest that tremelimumab monotherapy appears to have anti-tumour activity alongside a manageable safety profile in an advanced cancer population. While response rates are generally low (approximately 10%), in those patients who do respond the responses are generally durable, lasting several months. The enhanced AUC and exposure of the tremelimumab 10 mg/kg Q4W regimen may enhance efficacy while retaining a manageable safety profile.

Although limited in scope, the emerging data for the combination of MEDI4736 plus tremelimumab suggests an acceptable and manageable safety profile. There are early signs of clinical efficacy, and data in the literature from combinations of the same class of drugs showed higher response rates than those obtained with single-agent therapy, with responses that appear to be rapid and deep. Also, responses to the combination therapy were generally durable and were observed even in patients whose treatment was terminated early because of AEs (Wolchok et al 2013).

For patients with PD-L1-negative tumours, the risk-benefit assessment favours the proposed enrolment of these patients into the MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736 plus tremelimumab in Sub-study B of this study.

All patients will be closely monitored and are able to stop treatment at any time if they choose to do so, or if the investigator judges it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for delaying an infusion or permanently stopping MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736 combined with tremelimumab are provided.

Finally, the safety of patients in this study will be assessed by an Independent Data Monitoring Committee (IDMC) via ongoing safety assessments. The committee will meet approximately 6 months after the study has started or 20 patients have been randomised to the combination arm (whichever comes first) to review the safety data from the study. The IDMC will meet approximately every 6 months thereafter. In addition for Sub-study B, an interim contribution of components analysis may be reviewed by the IDMC to determine whether the MEDI4736+tremelimumab arm is superior to each of the MEDI4736 monotherapy and tremelimumab monotherapy arms in turn. If the MEDI4736+tremelimumab arm is superior to either or both of the monotherapy arms, then the applicable monotherapy arms may be dropped from Sub-study B. If either or both monotherapy arms are dropped any patients on treatment will have the opportunity to remain on treatment if they are gaining clinical benefit and if, after discussion with their treating physician, it is felt that this is the best treatment option for them.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
Sub-study A (PD-L1-positive population) To assess the efficacy of MEDI4736 monotherapy compared with Standard of Care in terms of OS and PFS Sub-study B (PD-L1-negative population) To assess the efficacy of MEDI4736+tremelimumab treatment compared with Standard of Care in terms of OS and PFS	OS[a] PFS using investigator assessments according to RECIST 1.1[a,b]

a In each of the Sub-studies A and B the assessment of PFS and OS will be considered co-primary objectives.
b The co-primary analysis of PFS will be based on programmatically-derived PFS based upon investigator assessment. For the analyses to be conducted, see Section 12.2.2.

OS Overall survival; PD-L1 Programmed death ligand 1; PFS Progression free survival; RECIST Response Evaluation Criteria In Solid Tumours.

2.2 Secondary objectives

The following are the secondary objectives in Sub-study A (MEDI4736 monotherapy versus Standard of Care) and Sub-study B (MEDI4736+tremelimumab versus Standard of Care):

Secondary Objective:	Outcome Measure:
To further assess the efficacy in terms of: OS12, ORR, DoR, APF6, APF12 and PFS2	OS12 ORR using investigator assessments according to RECIST 1.1[a] DoR using investigator assessments according to RECIST 1.1[a] APF6 and APF12 using investigator assessments according to RECIST 1.1[a] PFS2 as defined by local standard clinical practice
To assess the safety and tolerability profile	Adverse events, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, haematology and urinalysis
To assess the PK of MEDI4736 and tremelimumab	Concentration of PK in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling)
To investigate the immunogenicity of MEDI4736 and tremelimumab	ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed])

Secondary Objective:	Outcome Measure:
To assess symptoms and health-related QoL using EORTC QLQ-C30 v3 and LC13	EORTC QLQ-C30: Time to symptom deterioration (fatigue, pain, nausea/vomiting, dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea). Time to QoL/function deterioration (physical function; role function; emotional function; cognitive function; social function and global health status/QoL) LC13: Time to symptom deterioration (dyspnoea, cough, haemoptysis, chest pain, arm/shoulder pain, other pain) Changes in World Health Organisation Performance Status will also be assessed
Sub-study B (PD-L1-negative population) To evaluate the efficacy of MEDI4736+tremelimumab treatment compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy	PFS[a], ORR[a] and DoR[a] using investigator assessments according to RECIST 1.1, and OS

a Analysis of ORR, DoR, APF6 and APF12 will be based upon investigator assessment. For the analyses to be conducted, see Sections 12.2.3, 12.2.4, 12.2.5 and 12.2.6.

ADA Anti-drug antibody; APF6 Proportion of patients alive and progression free at 6 months from randomisation; APF12 Proportion of patients alive and progression free at 12 months from randomisation; DoR Duration of response; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; LC13 Lung Cancer Module; ORR Objective response rate; OS12 Proportion of patients alive at 12 months from randomisation; PFS Progression free survival; PFS2 Time from randomisation to second progression; PK Pharmacokinetic(s); QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumours; WHO World Health Organisation.

In Sub-study B, PFS in MEDI4736+tremelimumab arm will be compared to each of the MEDI4736 and tremelimumab monotherapy arms as part of the contribution of components analysis. This analysis is planned to be performed when approximately 158 PFS events are observed in the MEDI4736+tremelimumab and tremelimumab monotherapy arms. However, for practical considerations, if this time is close to the time of the final PFS analysis, the contribution of components analysis will be conducted at the time of the final PFS analysis. This is considered a secondary objective of the study.

2.3 Exploratory objectives

The following exploratory objectives will be addressed in Sub-studies A and B:

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE Adverse event; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; IFN Interferon; IL Interleukin; ORR Objective response rate; OS Overall survival; PD-L1 Programmed death ligand 1; PDx Pharmacodynamic(s); PFS Progression free survival; PK Pharmacokinetic(s).

With regards to PD-L1 expression determined by immunohistochemistry, this will be reported in the Clinical Study Report (CSR). CCI

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This study is a Phase III, randomised, open label, multi-centre study assessing the efficacy and safety of MEDI4736 versus Standard of Care in NSCLC patients with PD-L1-positive tumours and the combination of MEDI4736 plus tremelimumab (MEDI4736+tremelimumab) versus Standard of Care in NSCLC patients with PD-L1-negative tumours. The study will enrol male and female patients with locally advanced or metastatic NSCLC (Stage IIIB-IV), who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen for NSCLC. Patients with known EGFR tyrosine kinase (TK) activating mutations and anaplastic lymphoma kinase (ALK) rearrangements are not eligible for the study (prospective testing is not planned within this study).

Approximately 1300 patients will be recruited, with approximately 610 patients expected to be randomised (126 patients in Sub-study A and 480 patients in Sub-study B) at approximately 250 sites worldwide. The original study design intended to recruit 250 patients to Sub-study A. However, due to low patient accrual, the recruitment to Sub-study A was closed in Q1 2016 at which time 126 patients had been randomised. As a result, the analysis plan for Sub-study A was updated and is presented in Protocol Amendment 6.0, dated 31 August 2016.

Patients will be randomised in a 1:1 ratio in Sub-study A and a 3:2:2:1 ratio (MEDI4736+tremelimumab:MEDI4736:Standard of Care:tremelimumab) in Sub-study B.

Sub-study A (patients with PD-L1-positive tumours):

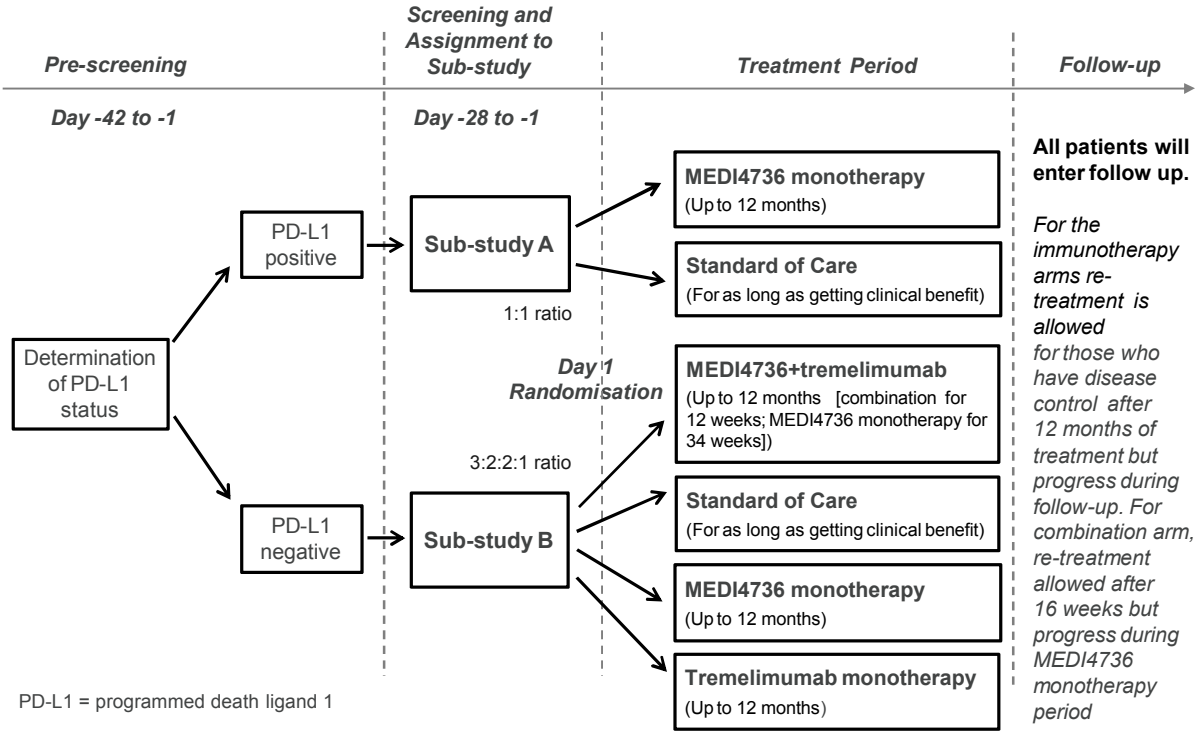
- MEDI4736 (10 mg/kg Q2W iv for up to 12 months) (approximately 60 patients)
- Standard of Care (restricted to the erlotinib, gemcitabine or vinorelbine) (approximately 60 patients). For each agent 4 weeks equates to 1 cycle of treatment.
  - Erlotinib: 150 mg once daily as a tablet for oral administration taken at least 1 hour before or 2 hours after the ingestion of food
  - Gemcitabine: 1000 mg/m^2 iv over 30 minutes on Days 1, 8, and 15 of a 28-day cycle
  - Vinorelbine: 30 mg/m^2 iv on Days 1, 8, 15 and 22 of a 28-day cycle.

Sub-study B (patients with PD-L1-negative tumours):

- MEDI4736+tremelimumab (MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg Q4W iv for up to 12 weeks [4 doses]) then MEDI4736 alone (10 mg/kg Q2W iv, starting at Week 16, for 34 weeks [18 doses]) (180 patients)
- Standard of Care (see under Sub-study A) (120 patients)
- MEDI4736 (10 mg/kg Q2W iv for up to 12 months) (120 patients)
- Tremelimumab (10 mg/kg Q4W iv for 24 weeks then Q12W for 24 weeks) (60 patients).

The sub-studies may not run concurrently with the start and completion of recruitment potentially occurring at different time points. Assignment to the applicable sub-study will be preceded by the Pre-screening Period during which assessment of the patient's PD-L1 status, based on a tumour sample, will take place. After confirmation of PD-L1 status, patients will enter the main Screening Period within their assigned sub-study if it remains open for recruitment. The study design is shown in diagram form in Figure 2.

Figure 2 Study design schema



Study procedures at Screening and during the Treatment Period for MEDI4736 monotherapy in Sub-studies A and B are presented in Table 3, and for tremelimumab monotherapy and MEDI4736+tremelimumab in Sub-study B in Table 4 and Table 5. Follow-up procedures for patients who have completed MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab and achieved disease control, and for

patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab due to toxicity or a reason other than confirmed PD are presented in Table 6. Follow-up procedures for patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab due to confirmed PD are presented in Table 7. Study procedures for patients treated with vinorelbine or gemcitabine in the Standard of Care arm are presented in Table 8. Study procedures for patients treated with erlotinib in the Standard of Care arm are presented in Table 9. Follow-up procedures for patients treated with Standard of Care are presented in Table 10.

Patients must have histologically- or cytologically-documented Stage IIIB/Stage IV NSCLC (according to Version 7 of the International Association for the Study of Lung Cancer (IASLC) Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology]), or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease). Patients with advanced or metastatic NSCLC must have received at least 2 prior systemic treatment regimens to be eligible including a platinum-based chemotherapy regimen.

PD-L1 expression will be determined for all patients prior to randomisation. Patients will be assigned to Sub-study A and Sub-study B respectively based on PD-L1 tumour expression status (PD-L1 positive versus PD-L1 negative [based on an archival tumour sample or a recent tumour biopsy]). Patients will be stratified at randomisation based on the Standard of Care treatment that they would be administered if randomised to the Standard of Care arm (2 categories: gemcitabine/vinorelbine versus erlotinib) and histology (2 categories: squamous versus all other).

The primary objective of this study is to assess the efficacy of MEDI4736 monotherapy (patients with PD-L1-positive tumours) and MEDI4736+tremelimumab (patients with PD-L1-negative tumours) compared with Standard of Care in terms of OS and PFS (per RECIST 1.1 as assessed by the investigator).

For Sub-study B, an interim analysis for OS will be performed. The purpose of the OS interim analysis is to demonstrate superiority to support the primary objective in terms of OS.

For Sub-study B, a contribution of components analysis will be performed when approximately 158 PFS events are observed in the MEDI4736+tremelimumab and tremelimumab monotherapy arms. However, for practical considerations, if this time is close to the time of the final PFS analysis, the contribution of components analysis will be conducted at the time of the final PFS analysis. The purpose of this analysis is to compare the monotherapy and combination dosing regimens to determine if the combination therapy (ie, MEDI4736+tremelimumab) is more efficacious than each of the monotherapy arms. As these treatment comparisons are secondary and serve a different purpose to that of the primary comparisons, they are not included in the multiple testing procedure for the primary comparisons, and an alpha of 0.05 will be used for either PFS or OS without multiplicity adjustment.

If the contribution of components analysis is performed prior to the final PFS analysis and the MEDI4736+tremelimumab arm is superior to either of the monotherapy arms, then that monotherapy arm may be dropped from the study and all patients on that treatment will be discontinued. However, any patients on that treatment will have the opportunity to remain on treatment if they are gaining clinical benefit and if, after discussion with their treating physician, it is felt that this is the best treatment option for them.

Sub-study A: Treatment with MEDI4736 10 mg/kg will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a Q2W schedule for up to 12 months. Treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Patients who have discontinued treatment due to toxicity, symptomatic deterioration or who have commenced subsequent anti-cancer therapy will be followed up until confirmed disease progression or death (whichever occurs first). Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Sub-study B: Treatment with MEDI4736 or tremelimumab monotherapy, or the combination of MEDI4736+tremelimumab will commence on Day 1 following randomisation after confirmation of eligibility. MEDI4736 will continue on a 10 mg/kg Q2W schedule when given as monotherapy for up to 12 months and tremelimumab when given as a monotherapy, will continue on a 10 mg/kg Q4W schedule for 24 weeks then Q12W for a further 24 weeks. MEDI4736+tremelimumab in combination will be administered from Day 1 on a Q4W schedule up to 12 weeks (4 doses of MEDI4736 20 mg/kg and tremelimumab 1 mg/kg) after which MEDI4736 10 mg/kg alone will be administered on a Q2W schedule for 34 weeks starting at Week 16 (18 doses).

In the monotherapy arms in Sub-study B, treatment should be discontinued prior to 12 months (MEDI4736 monotherapy) or 48 weeks (tremelimumab monotherapy) if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Patients who have discontinued treatment due to toxicity, symptomatic deterioration or who have commenced subsequent anti-cancer therapy will be followed up until confirmed disease progression or death (whichever occurs first).

Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

In the combination arm, if a patient experiences PD, retreatment with the combination regimen (MEDI4736+ tremelimumab) is allowed. Retreatment in the combination arm can

only occur if PD, with or without confirmation, occurs during the MEDI4736 monotherapy portion or after completion of 12 months of therapy. During the retreatment period, the patient would resume MEDI4736 dosing at 20 mg/kg Q4W as during the initial induction period, along with 1 mg/kg of tremelimumab Q4W for 4 doses. Monotherapy with MEDI4736 would then resume at 10 mg/kg Q2W 4 weeks after the last combination dose is administered for as long as the investigator judges they are gaining clinical benefit.

Both Sub-study A and B: Treatment in the Standard of Care arm will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a 4-weekly schedule until PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur.

Tumour assessments using computed tomography (CT)/magnetic resonance imaging (MRI) will be performed every 8 weeks at the times specified in Table 3, Table 4, Table 6 and Table 7 for patients receiving MEDI4736 and tremelimumab monotherapy, Table 5, Table 6 and Table 7 for patients receiving MEDI4736+tremelimumab, and Table 8 (for patients receiving gemcitabine or vinorelbine), Table 9 (for patients receiving erlotinib), and Table 10 (follow-up period for all patients in the Standard of Care arm) for patients receiving Standard of Care. The baseline assessment should be performed within the 28 days prior to randomisation. Response Evaluation Criteria In Solid Tumours 1.1 measurements (using investigator assessments) will be used to derive the co-primary variable of PFS and secondary variables of ORR, DoR, APF6, APF12 and PFS2. Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD.

Once a patient has had objective progression recorded and has discontinued study drug, the patient will be followed up for survival status every 2 months until death, withdrawal of consent or the final DCO.

Sensitivity analyses will be performed on PFS, ORR and DoR based on tumour information recorded in the clinical database by the investigator according to RECIST 1.1 (Sub-study B). See Section 6.3 and Appendix F for further information regarding RECIST tumour assessments in this study.

The study flow charts are presented in Figure 3 (for patients randomised to MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab) and Figure 4 (for patients randomised to Standard of Care).

It is important to follow the assessment schedules as closely as possible. The schedule of study procedures at Screening and during the Treatment Period for MEDI4736 monotherapy is presented in Table 3, for tremelimumab monotherapy in Table 4 and for MEDI4736+tremelimumab in Table 5. The schedule of follow-up procedures for patients who have completed MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab and achieved disease control, and patients who have discontinued

MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab due to toxicity or a reason other than confirmed PD is presented in Table 6. The schedule of follow-up procedures for patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab due to confirmed PD is presented in Table 7.

The schedule of study procedures for patients treated with vinorelbine or gemcitabine in the Standard of Care arm is presented in Table 8. The schedule of study procedures for patients treated with erlotinib in the Standard of Care arm is presented in Table 9. The schedule of follow-up procedures for patients treated with Standard of Care is presented in Table 10.

Every effort should be made to obtain accurate follow-up information on patients whose PFS and OS data were not accurately recorded. For example, in the case of PFS, the local investigator could provide their clinical assessment of progression if care transfers elsewhere, and for OS an effort should be made to continue to follow and use death registries where necessary.

Guidelines for the management of toxicities are described in Section 5.5.3.

CCI

Treatment delays

All visits should be conducted based on the schedules provided in Table 3 to Table 10, unless otherwise indicated.

For all treatment arms

- Tumour efficacy (RECIST 1.1) assessments dates are not affected by dose delays, and remain as originally scheduled, because they are based on the date of randomisation (not the date of therapy).
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures required for dosing should be performed within 3 days prior to dosing.

For MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab combination arms

Patients may delay dosing under certain circumstances:

- Dosing may be delayed due to either an immune or a non-immune-related AE (irAE) as per Toxicity Management Guidelines (Refer to Section 5.5.3).
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

- Dosing intervals of subsequent cycles in the combination arm may be shortened as clinically feasible and in line with the treatment windows in order to gradually align treatment cycles with the schedule of tumour efficacy (RECIST 1.1) assessments.

Independent Data Monitoring Committee

An IDMC will be convened and will meet approximately 6 months after the study has started or 20 patients have been randomised to the combination arm on Sub-study B (whichever comes 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. The IDMC will also review:

- The interim analysis for OS on Sub-study B (see Section 12.2.14)
- The contribution of components analysis for the immunotherapy arms if this analysis occurs before the primary PFS analysis.

All patients who receive a dose of study treatment will be evaluated for safety and tolerability. Enrolment will continue unless there is an unexpected safety concern. The study may be adjusted or suspended depending on the IDMC review outcome.

Details on the IDMC are provided in Section 12.4 and full details of the IDMC procedures and processes can be found in the IDMC Charter.

End of Analysis Portion of Study

At the time of the final DCO, the analysis portion of the clinical study will have been completed and all patients remaining in the study will be considered to have completed the analysis portion of the study.

Patients in OS follow-up (progressed and have completed treatment) will be considered to have completed the study. Patients in progression-free follow up (patients who have completed treatment and have not progressed and who are still potentially eligible for retreatment) may decide to continue in the study in progression-free follow up. These patients would therefore remain eligible for possible future re-treatment upon progression if they meet re-treatment criteria and the investigator judges that the patient will gain clinical benefit. Patients already receiving re-treatment at the time of final DCO for the study may continue receiving investigational product if the investigator judges that they are gaining clinical benefit.

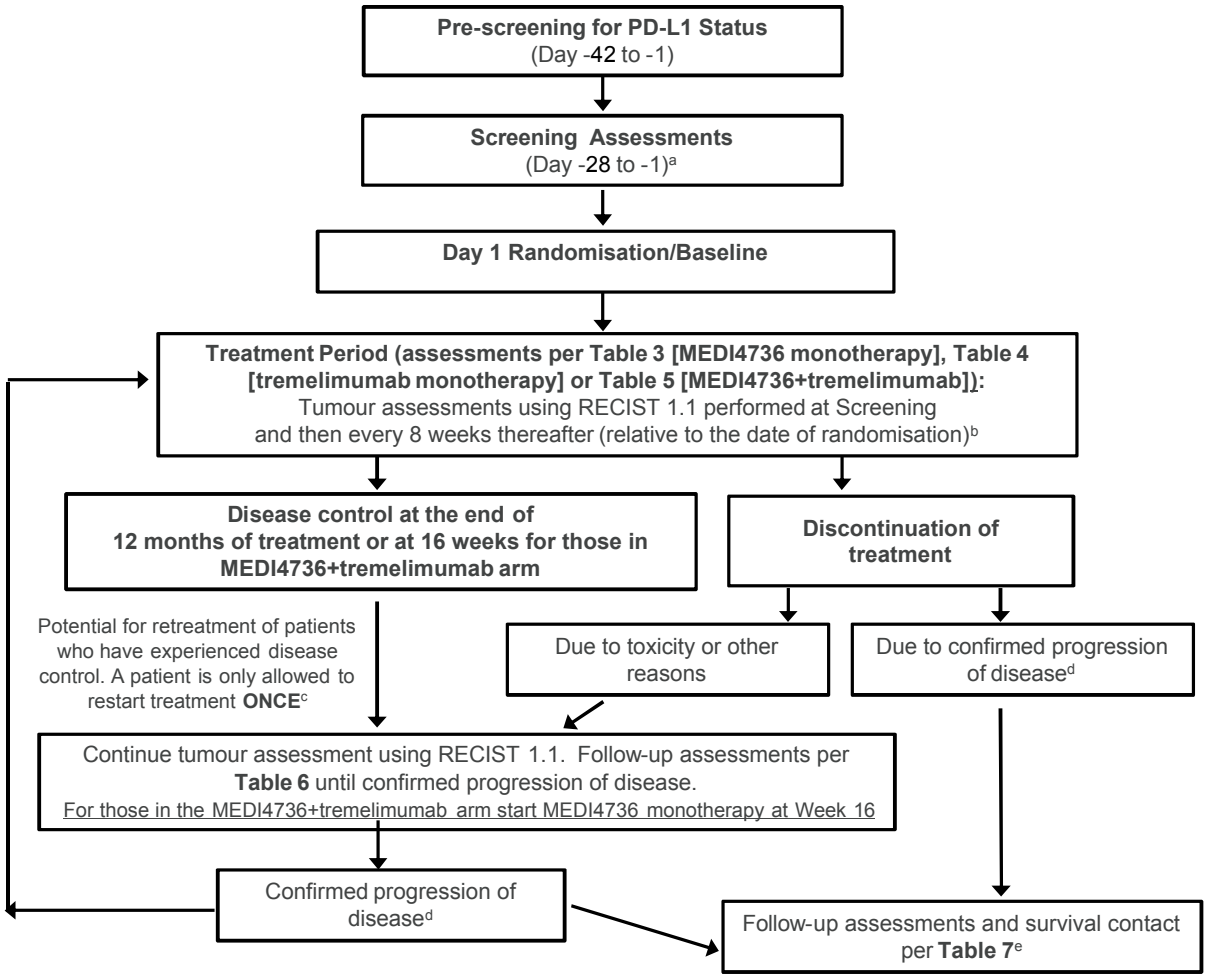
Scans will be collected in accordance with local clinical practice. Patients in progression-free follow-up after the final DCO are to undergo sampling for local laboratory assessments in such a way that continued per-protocol re-treatment eligibility can be properly determined. For patients receiving re-treatment after final DCO, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during treatment in order to manage AEs in

accordance with the toxicity management guidelines (Refer to Section 5.5.3). All data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

For patients who either continue to receive treatment or begin re-treatment after the time of the final DCO, investigators will report all serious adverse events (SAEs) to AstraZeneca/MedImmune patient safety until 90 days after investigational product is discontinued. Following the final DCO, SAE reporting applies only to patients who are active on the drug and within 90 days post the last dose. In addition, in patients who are still in progression-free follow-up at the final DCO and who are eligible for future re-treatment (ie, the patient was randomised to investigational product, completed the initial 12 month treatment period and had SD, PR or CR at completion of 12 months of treatment), notification must be sent to QuintilesIMS if the patient dies (via the statement of death CRF) or if the patient goes onto receive another alternate systemic anti-cancer therapy and thus becomes ineligible for re-treatment.

In the event that a roll-over or safety extension study will become available, patients currently receiving treatment with study drug or patients in progression-free follow-up may be transitioned to such a study, and the current study would 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.

Figure 3 Study flow chart (for patients randomised to MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab)



a Screening assessments can be performed in a step-wise process. The baseline tumour assessment should be performed within the 28 days prior to randomisation.

b In the monotherapy arms and during the first 4 cycles of the combination arm, disease progression requires confirmation and the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Administration of study treatment will continue between the initial assessment of progression and confirmation for progression. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 4.3. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study treatment.

c In the monotherapy arms, patients who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 12-month/48-week treatment period may restart study treatment upon evidence of PD (according to RECIST 1.1) with or without confirmation during follow-up. Patients in the MEDI4736+tremelimumab arm who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 4th cycle (Week 16, 4 weeks after the last dose of combination treatment) may restart combination treatment upon evidence of PD (according to RECIST 1.1), with or without confirmation, during the MEDI4736 monotherapy part of the combination schedule. Before restarting study treatment, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and

exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3. To restart study treatment the patient must not have received an intervening systemic anti-cancer therapy post-study treatment discontinuation. Patients should have a baseline tumour assessment within 28 days before restarting study treatment, all further scans should occur every 8 weeks (relative to the date of restarting study treatment). Patients who continue to receive re-treatment after the final DCO should receive scans/RECIST and other assessments as per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3).

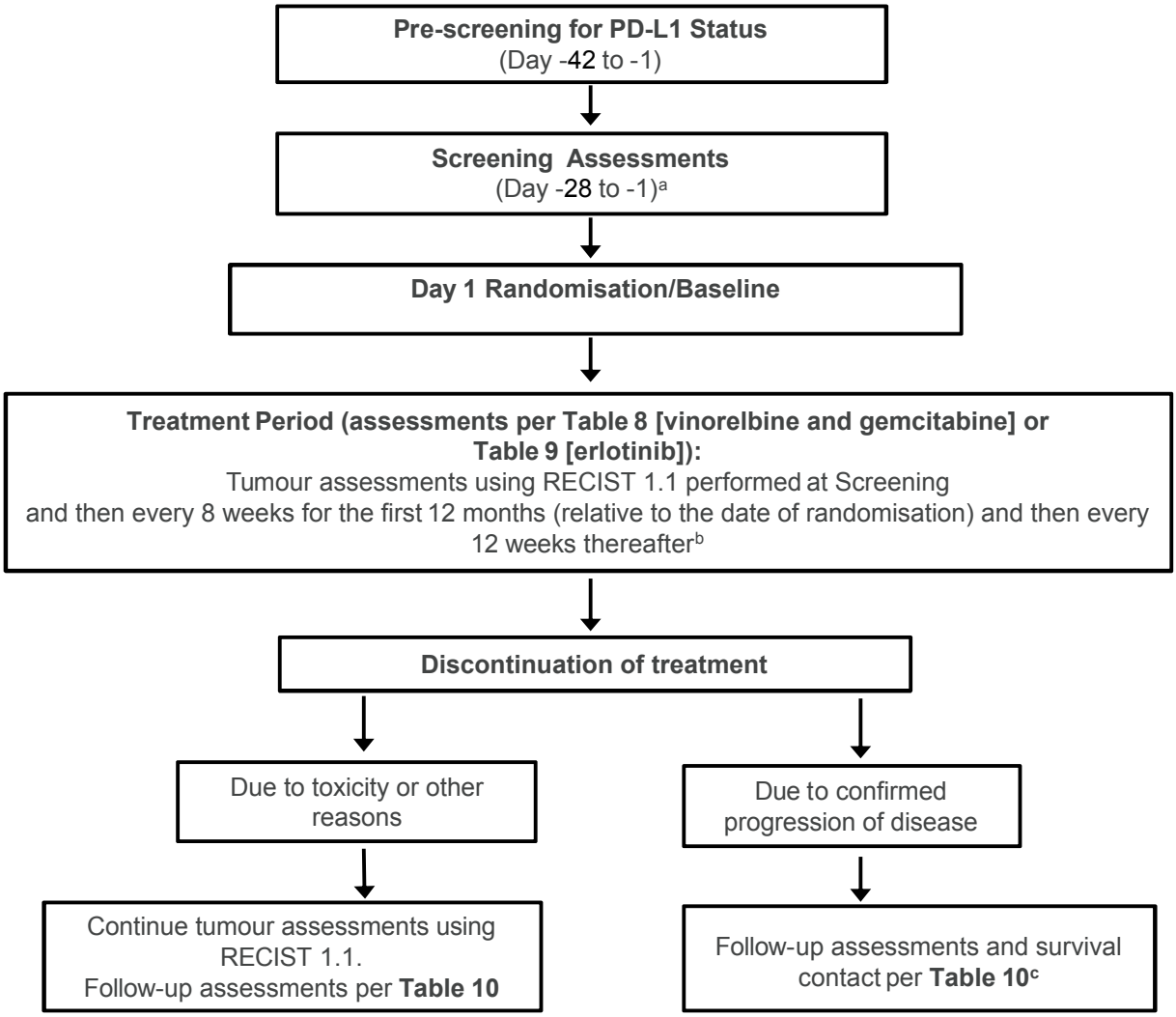
d Patients with confirmed PD that continue to receive study treatment at the discretion of the investigator (following consultation with the sponsor) can receive study treatment for a maximum of 12 months during the initial treatment period but for as long as the investigator judges they are gaining clinical benefit in the retreatment phase. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3. The same exceptions as noted in footnote b apply. Patients will follow the assessments in Table 3, Table 4 or Table 5 including tumour assessments every 8 weeks (relative to the date of randomisation) until study treatment is stopped. Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period). Patients who continue to receive re-treatment after the final DCO should receive scans/RECIST and other assessments per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3).

e Patients with confirmed PD that discontinue study treatment, should have scans conducted according to local standard clinical practice (see Section 6.2.2.2) until the patient commences a new treatment (these scans are optional).

Note: It is estimated the DCO for the final analysis of overall survival will take place approximately 24 months after the first patient is randomised on Sub-study A and 27 months after the first patient is randomised on Sub-study B. At this time point, patients who are receiving study treatment can either choose to discontinue from the study or where the investigator judges patients are gaining clinical benefit, patients may continue to receive study treatment. For patients who do continue to receive study treatment beyond the time of the final DCO, investigators will only report SAEs to AstraZeneca Patient Safety until 90 days after study drug is discontinued. Any non-serious AEs occurring or ongoing after the time of this final DCO are to be followed up at the investigator's discretion and per local standard of care.

AE Adverse event; CR Complete response; DCO Data cut-off; PD Progression of disease; PD-L1 Programmed death ligand 1; PR Partial response; RECIST Response Evaluation Criteria In Solid Tumours; SAE Serious adverse event; SD Stable disease.

Figure 4 Study flow chart (for patients randomised to Standard of Care)



a Screening assessments can be performed in a step-wise process. The baseline tumour assessment should be performed within the 28 days prior to randomisation.

b A confirmatory scan is required for all patients even if a subsequent treatment is started. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment through PD in the Standard of Care arm is at the investigator's discretion. In cases of unequivocal progression the investigator should discontinue treatment, where it is uncertain if disease has progressed the investigator should decide whether (if in the absence of clinically significant deterioration) to continue the patient on treatment until progression has been confirmed. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 4.3.

c Patients with confirmed PD that discontinue study treatment, should have scans conducted according to local standard clinical practice (see Section 6.2.2.2) until the patient commences a new treatment (these scans are optional).

Note: It is estimated the DCO for the final analysis of overall survival will take place approximately 24 months after the first patient is randomised on Sub-study A and 27 months after the first patient is randomised on Sub-study B. At this time point, patients who are receiving study treatment can either choose to discontinue from the study or where the investigator judges patients are gaining clinical benefit, patients may continue to receive study treatment. For patients who do continue to receive study treatment beyond the time of the final DCO, investigators will only continue to report all SAEs to AstraZeneca/MedImmune Patient Safety until 30 days after Standard of Care treatment is discontinued and any SAE or non-serious AE that is ongoing at the time of this DCO must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.
AE Adverse event; DCO Data cut-off; PD Progression of disease; PD-L1 Programmed death ligand 1; RECIST Response Evaluation Criteria In Solid Tumours; SAE Serious adverse event.

Table 3 Schedule of study procedures for the MEDI4736 monotherapy arm in Sub-study A and Sub-study B: Screening and Treatment Period (up to 12 months, maximum of 26 doses. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**							
			Random-isation					**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**15**	**29**	**43**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**2**	**4**	**6**	**8[b]**	**10, 12, 14, 16, etc**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**
				---------- (±3 days[b]) ----------						**--- (±7 days) ---**
Written pre-screening informed consent/assignment of patient identification number (Section 6.2)	X									
Preliminary eligibility fulfilment (investigator's opinion)	X									
Demography and history of tobacco and alcohol use	X									
Previous treatments for NSCLC	X									
Archival (>3 years) FFPE tumour tissue sample for PD-L1 assay (optional) (see Section 6.7)	X									
Newly acquired or archival (≤3 years) formalin-fixed tumour biopsy for PD-L1 assay (mandatory) (see Section 6.7)	X									
Written sub-study informed consent (Note: Patients are required to re-consent to continue study drug when treated through progression and to restart study drug following initial disease control [See Section 8.4])		X								
Formal verification of eligibility criteria		X	X							
Randomisation (see Section 5.2)			X							
Patient questionnaires (patient reported outcomes) (see Section 6.5)		X	X		X		X			X

Table 3 Schedule of study procedures for the MEDI4736 monotherapy arm in Sub-study A and Sub-study B: Screening and Treatment Period (up to 12 months, maximum of 26 doses. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**							
			Random-isation					**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**15**	**29**	**43**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**2**	**4**	**6**	**8[b]**	**10, 12, 14, 16, etc**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**
				(±3 days[b])						**(±7 days)**
CCI										
					CCI					
Medical and surgical history		X								
Hepatitis B and C; HIV		X								
Height		X								
Urine hCG or serum βhCG		X	X	X	X	X	X	X		
Kit assignment and MEDI4736 administration			X	X	X	X	X	X		
Physical examination		X	X	X	X	X	X		X	
Vital signs (BP, pulse [pre- and post-infusion], respiratory rate, temperature, oxygen saturation; see Section 6.4.8)		X	X	X	X	X	X	X		
Weight		X	X		X		X		X	
Electrocardiogram (see Section 6.4.7)[d]		X	X[d]						X[d] (Week 12 only)	
Adverse event/serious adverse event assessment (see Section 6.4.3)	X[e]	X	X	X	X	X	X	X		
Concomitant medications		X	X	X	X	X	X	X		

Table 3 Schedule of study procedures for the MEDI4736 monotherapy arm in Sub-study A and Sub-study B: Screening and Treatment Period (up to 12 months, maximum of 26 doses. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**							
			Random-isation					**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**15**	**29**	**43**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**2**	**4**	**6**	**8[b]**	**10, 12, 14, 16, etc**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**
				---------- (±3 days[b]) ----------						**--- (±7 days) ---**
Palliative radiotherapy			As clinically indicated (see Section 5.1) →							
World Health Organisation performance status		X	X	X	X	X	X		X	
Serum chemistry[f]		X	X	X	X	X	X	X		
Amylase, lipase (where available)[f]		X	X		X		X		X	
Thyroid function tests (TSH and T3 and T4) (see Section 6.4.9)		X	X		X		X		X	
Haematology[f]		X	X	X	X	X	X	X		
Urinalysis[g]		X	X		X		X		X	
Coagulation parameters[h]		X		As clinically indicated →						
Pharmacokinetic assessment (see Section 6.6.1)[i]			X (and EOI)				X			X (Weeks 24 [and EOI] and 48 only)
Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) (see Section 6.6.2)[i]			X				X			X (Weeks 24 and 48 only)

Table 3 Schedule of study procedures for the MEDI4736 monotherapy arm in Sub-study A and Sub-study B: Screening and Treatment Period (up to 12 months, maximum of 26 doses. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	Pre-screening for PD-L1 status ONLY	Screening	All assessments to be performed pre-infusion unless stated otherwise							
			Random-isation					Every 2 weeks	Every 4 weeks	Every 8 Weeks
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**15**	**29**	**43**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**2**	**4**	**6**	**8[b]**	**10, 12, 14, 16, etc**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**
				(±3 days[b])						**(±7 days)**
sPD-L1 concentration (to assess target engagement) (see Section 6.7)[i]			X				X			X (Weeks 24 and 48 only)
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) (see Section 6.7)			X		X				X (Week 12 only)	
CCI										
CCI										
Tumour assessment (CT or MRI)[j,k,l]		X					X			X

a Every effort should be made to minimise the time between randomisation and starting treatment. It is recommended that patients commence study treatment as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS/IWRS system) and no later than 48 hours after randomisation.

b At Week 8 the allowed window for the tumour assessment is ±7 days.

c CCI

d ECGs: At Screening digital ECGs should be performed in triplicate with a 2- to 5-minute time lag between each measurement. During treatment, mandatory ECGs are performed on Day 1 and at Week 12; only a single digital ECG measurement is required at these visits. On Day 1 and Week 12, ECGs should be taken 30 to 60 minutes before study drug infusion and at least 1 time point 0 to 3 hours after infusion. ECGs should be performed at other times if clinically indicated.

e For SAEs that occur in the pre-screening period additional information such as medical history may be requested.

f If Screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for urea and electrolytes, full blood count and liver function tests must be available before commencing any infusion with study drug. Gamma glutamyltransferase tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and as clinically indicated. Creatinine clearance, magnesium, amylase, lipase, and uric acid tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and every 4 weeks thereafter.

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

h Coagulation tests: Prothrombin time, APTT and INR only performed at Screening and as clinically indicated.

i **PK, ADA and sPD-L1** samples to be collected at Day 1, Week 8, Week 24 and Week 48. **PK samples**: At each collection, patients will have 1 sample drawn. On Day 1 and Week 24, samples will be collected before and after infusion. At other visits, only a pre-dose sample is required. Pre-dose samples are drawn within 60 minutes prior to the start of infusion and EOT samples within 10 minutes after end of infusion. **ADA samples**: At each collection, 1 sample will be drawn. All samples should be collected pre-dose (ie, within 60 minutes prior to the start of the infusion). **sPD-L1 samples**: At each collection, 1 sample only is drawn from patients. All samples should be collected pre-dose only (ie, within 60 minutes prior to the start of the infusion).

j RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up. The baseline assessment should be performed within the 28 days prior to randomisation and ideally as close as possible before the start of MEDI4736. Follow-up assessments will be performed every 8 weeks ± 1 week for the first 48 weeks (relative to the date of randomisation) while on treatment until confirmed objective disease progression per RECIST 1.1. The confirmatory scans should be performed to preferably occur at the next scheduled visit (relative to the date of randomisation) and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomisation). All confirmatory scans should be databased. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 4.3. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug.

k Patients who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 12-month treatment period may restart MEDI4736 upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up. Before restarting MEDI4736, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3. To restart MEDI4736 the patient must not have received an intervening systemic anti-cancer therapy post discontinuation of MEDI4736. Patients should have a baseline tumour assessment within 28 days prior to restarting MEDI4736, all further scans should occur every 8 weeks ± 1 week (relative to the date of restarting MEDI4736), or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment with MEDI4736 in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3).

l Patients with confirmed PD during the initial treatment period that continue to receive MEDI4736 at the discretion of the investigator (following consultation with the sponsor) can receive MEDI4736 for a maximum of 12 months. Retreatment may continue as long as the investigator judges the patient to be gaining clinical benefit. Patients will have scans every 8 weeks ± 1 week (relative to the date of randomisation) until treatment with MEDI4736 is stopped, or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment with MEDI4736 in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3). Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug. Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Note: If a patient has a delay to an infusion of MEDI4736 all assessments should be conducted relative to the date of randomisation.

Note: For 're-treatment' patients who go on to have subsequent treatment prior to the final DCO, the same assessments should be done as in the first 12-month treatment period with the exception of the PK, ADA, sPD-L1, and PGx, assessments which do not need to be collected a second time. This includes all assessments listed under 'screening' and 'randomisation' which should be completed again following the decision to re-treat. Additionally, if feasible or clinically indicated, a biopsy at entry to re-treatment may optionally be collected.

ADA Anti-drug antibody; APTT Activated partial thromboplastin time; BP Blood pressure; CR Complete response; CT Computed tomography; ECG Electrocardiogram; EOI End of infusion; FFPE Formalin-fixed paraffin-embedded; hCG Human chorionic gonadotropin; HIV Human immunodeficiency virus; INR International normalised ratio; IVRS/IWRS Interactive Voice/Web Response System; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NSCLC Non-small cell lung cancer; PD Progression of disease; PGx Pharmacogenetic(s); PK Pharmacokinetics; PR Partial response; RECIST Response Evaluation Criteria In Solid Tumours; SD Stable disease; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

Table 4 Schedule of study procedures for the tremelimumab monotherapy arm in Sub-study B: Screening and Treatment Period (up to 48 weeks, maximum of 9 doses of tremelimumab. Last infusion at Week 48)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**						
		Screening	**Randomisation**			**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**	**24, 36 and 48**
				---------- (±3 days[b]) ----------			**------- (±7 days) -------**	
Written pre-screening informed consent/assignment of patient identification number (Section 6.2)	X							
Preliminary eligibility fulfilment (investigator's opinion)	X							
Demography and history of tobacco and alcohol use	X							
Previous treatments for NSCLC	X							
Archival (>3 years) FFPE tumour tissue sample for PD-L1 assay (optional) (see Section 6.7)	X							
Newly acquired or archival (≤3 years) formalin-fixed tumour biopsy for PD-L1 assay (mandatory) (see Section 6.7)	X							
Written sub-study informed consent (Note: Patients are required to re-consent to continue study drug when treated through progression and to restart study drug following initial disease control [See Section 8.4])		X						
Formal verification of eligibility criteria		X	X					
Randomisation (see Section 5.2)			X					
Patient questionnaires (patient reported outcomes) (see Section 6.5)		X	X	X	X			X
CCI [redacted]			[redacted]	[redacted]	[redacted]	[redacted]		
Medical and surgical history		X						

Table 4 Schedule of study procedures for the tremelimumab monotherapy arm in Sub-study B: Screening and Treatment Period (up to 48 weeks, maximum of 9 doses of tremelimumab. Last infusion at Week 48)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**						
		Screening	**Randomisation**			**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**	**24, 36 and 48**
				---------- (±3 days[b]) ----------			**------- (±7 days) -------**	
Hepatitis B and C; HIV		X						
Height		X						
Urine hCG or serum βhCG		X	X	X	X	X		
Kit assignment and tremelimumab administration (4-weekly for 24 weeks)			X	X	X	X		
Tremelimumab administration (12-weekly for 24 weeks)								X
Physical examination		X	X	X	X	X		
Vital signs (BP, pulse [pre- and post-infusion], respiratory rate, temperature, oxygen saturation; see Section 6.4.8)		X	X	X	X	X		
Weight		X	X	X	X	X		
Electrocardiogram (see Section 6.4.7)[c]		X[c]	X[c]			X[c] (Week 12 only)		
Adverse event/serious adverse event assessment (see Section 6.4.3)	X[d]	X	X	X	X	X		
Concomitant medications		X	X	X	X	X		
Palliative radiotherapy		As clinically indicated (see Section 5.1) →						
World Health Organisation performance status		X	X	X	X	X		

Table 4 Schedule of study procedures for the tremelimumab monotherapy arm in Sub-study B: Screening and Treatment Period (up to 48 weeks, maximum of 9 doses of tremelimumab. Last infusion at Week 48)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**						
		Screening	**Randomisation**			**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**	**24, 36 and 48**
				---------- (±3 days[b]) ----------			**------- (±7 days) -------**	
Serum chemistry[e]		X	X	X	X	X		
Amylase, lipase (where available)[e]		X	X	X	X	X		
Thyroid function tests (TSH and T3 and T4) (see Section 6.4.9)		X	X	X	X	X		
Haematology[e]		X	X	X	X	X		
Urinalysis[f]		X	X	X	X	X		
Coagulation parameters[g]		X	As clinically indicated →					
Pharmacokinetic assessment (see Section 6.6.1)[h]			X (and EOI)		X		X (Weeks 24 [and EOI] and 48 only)	
Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) (see Section 6.6.2)[h]			X		X		X (Weeks 24 and 48 only)	
sPD-L1 concentration (see Section 6.7)[h]			X		X		X (Weeks 24 and 48 only)	
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) (see Section 6.7)			X	X		X (Week 12 only)		

Table 4 Schedule of study procedures for the tremelimumab monotherapy arm in Sub-study B: Screening and Treatment Period (up to 48 weeks, maximum of 9 doses of tremelimumab. Last infusion at Week 48)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**						
		Screening	**Randomisation**			**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12, 16, 20, 24, 28, etc**	**16, 24, 32, 40 and 48**	**24, 36 and 48**
				---------- (±3 days[b]) ----------			------- (±7 days) -------	
CCI								
CCI								
Tumour assessment (CT or MRI)[i,j,k]		X			X		X	

a Every effort should be made to minimise the time between randomisation and starting treatment. It is recommended that patients commence study treatment as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS/IWRS system) and no later than 48 hours after randomisation.

b At Week 8 the allowed window for the tumour assessment is ±7 days.

c ECGs: At Screening, digital ECGs should be performed in triplicate with a 2- to 5-minute time lag between each measurement. During treatment, mandatory ECGs are performed on Day 1 and at Week 12; only a single digital ECG measurement is required at these visits. On Day 1 and Week 12, ECGs should be taken 30 to 60 minutes before study drug infusion and at least 1 time point 0 to 3 hours after infusion. ECGs should be performed at other times if clinically indicated.

d For SAEs that occur in the pre-screening period additional information such as medical history may be requested.

e If Screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for urea and electrolytes, full blood count and liver function tests must be available before commencing any infusion with study drug. Gamma glutamyltransferase tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and as clinically indicated. Creatinine clearance, magnesium, amylase, lipase, and uric acid tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and every 4 weeks thereafter.

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

g Coagulation tests: Prothrombin time, APTT and INR only performed at Screening and as clinically indicated.

h **PK, ADA and sPD-L1 samples** to be collected at Day 1, Week 8, Week 24 and Week 48. **PK samples:** At each collection, patients will have 1 sample drawn. On Day 1 and Week 24, samples will be collected before and after infusion. At other visits, only a pre-dose sample is required. Pre-dose samples are drawn within 60 minutes prior to the start of infusion and EOT samples within 10 minutes after end of infusion. **ADA samples**: At each collection, 1 sample will be drawn. All samples should be collected pre-dose (ie, within 60 minutes prior to the start of the infusion). **sPD-L1 samples**: At each collection, 1 sample only is drawn from patients. All samples should be collected pre-dose only (ie, within 60 minutes prior to the start of the infusion).

i RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up. The baseline assessment should be performed within the 28 days prior to randomisation and ideally as close as possible before the start of study treatment. Follow-up assessments will be performed every 8 weeks ± 1 week for the first 48

weeks (relative to the date of randomisation) while on treatment until confirmed objective disease progression per RECIST 1.1. The confirmatory scans should be performed to preferably occur at the next scheduled visit (relative to the date of randomisation) and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomisation). All confirmatory scans should be databased. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 4.3. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug.

j Patients who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 48-week treatment period may restart study drug upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up. Before restarting study drug, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3. To restart study drug the patient must not have received an intervening systemic anti-cancer therapy post discontinuation of study drug. Patients should have a baseline tumour assessment within 28 days prior to restarting study drug, all further scans should occur every 8 weeks ± 1 week (relative to the date of restarting study drug), or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3).

k Patients with confirmed PD during the initial treatment period who continue to receive study drug at the discretion of the investigator (following consultation with the sponsor) can receive study drug for a maximum of 48 weeks. Retreatment may continue as long as the investigator judges the patient to be gaining clinical benefit. Patients will have scans every 8 weeks ± 1 week (relative to the date of randomisation) until treatment with study drug is stopped, or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3). Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug. Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Note: If a patient has a delay to an infusion of study drug all assessments should be conducted relative to the date of randomisation.

Note: For 'retreatment' patients who go on to have subsequent treatment prior to the final DCO, the same assessments should be done as in the first 12-month treatment period with the exception of the PK, ADA, sPD-L1, and PGx, assessments which do not need to be collected a second time. This includes all assessments listed under 'screening' and 'randomisation' which should be completed again following the decision to re-treat. Additionally, if feasible or clinically indicated, a biopsy at entry to re-treatment may optionally be collected.

ADA Anti-drug antibody; APTT Activated partial thromboplastin time; BP Blood pressure; CR Complete response; CT Computed tomography; ECG Electrocardiogram; EOI End of infusion; FFPE Formalin-fixed paraffin-embedded; hCG Human chorionic gonadotropin; HIV Human immunodeficiency virus; INR International normalised ratio; IVRS/IWRS Interactive Voice/Web Response System; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NSCLC Non-small cell lung cancer; PD Progression of disease; PGx Pharmacogenetic(s); PK Pharmacokinetics; PR Partial response; RECIST Response Evaluation Criteria In Solid Tumours; SD Stable disease; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

Table 5 Schedule of study procedures for the MEDI4736+tremelimumab arm in Sub-study B: Screening and Treatment Period (up to 50 weeks, maximum of 22 doses of MEDI4736 and 4 doses of tremelimumab. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**							
		Screening	**Randomisation**				**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**85**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12**	**16, 18, 20, 22, 24, etc**	**16, 20, 24, 28, 32, etc**	**16, 24, 32, 40 and 48**
				(±3 days[b])					**(±7 days)**
Written pre-screening informed consent/assignment of patient identification number (Section 6.2)	X								
Preliminary eligibility fulfilment (investigator's opinion)	X								
Demography and history of tobacco and alcohol use	X								
Previous treatments for NSCLC	X								
Archival (>3 years) FFPE tumour tissue sample for PD-L1 assay (optional) (see Section 6.7)	X								
Newly acquired or archival (≤3 years) formalin-fixed tumour biopsy for PD-L1 assay (mandatory) (see Section 6.7)	X								
Written sub-study informed consent (Note: Patients are required to re-consent to continue study drug when treated through progression and to restart study drug following initial disease control [See Section 8.4])		X							

Table 5 Schedule of study procedures for the MEDI4736+tremelimumab arm in Sub-study B: Screening and Treatment Period (up to 50 weeks, maximum of 22 doses of MEDI4736 and 4 doses of tremelimumab. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**							
		Screening	**Randomisation**				**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**85**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12**	**16, 18, 20, 22, 24, etc**	**16, 20, 24, 28, 32, etc**	**16, 24, 32, 40 and 48**
				(±3 days[b])					**(±7 days)**
Formal verification of eligibility criteria		X	X						
Randomisation (see Section 5.2)			X						
Patient questionnaires (patient reported outcomes) (see Section 6.5)		X	X	X	X				X
CCI [redacted]									
CCI [redacted]									
Medical and surgical history		X							
Hepatitis B and C; HIV		X							
Height		X							
Urine hCG or serum βhCG		X	X	X	X	X	X		
Kit assignment and MEDI4736 20 mg/kg administration (4-weekly to Week 12)[d]			X	X	X	X			
Kit assignment and tremelimumab 1 mg/kg administration (4-weekly for 12 weeks[d]			X	X	X	X			

Table 5 Schedule of study procedures for the MEDI4736+tremelimumab arm in Sub-study B: Screening and Treatment Period (up to 50 weeks, maximum of 22 doses of MEDI4736 and 4 doses of tremelimumab. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**							
		Screening	**Randomisation**				**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**85**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12**	**16, 18, 20, 22, 24, etc**	**16, 20, 24, 28, 32, etc**	**16, 24, 32, 40 and 48**
				---------- (±3 days[b]) ----------					**----- (±7 days) -----**
Kit assignment and MEDI4736 10 mg/kg administration (2-weekly from Week 16)[d]							X		
Physical examination		X	X	X	X	X		X	
Vital signs (BP, pulse [pre- and post-infusion], respiratory rate, temperature, oxygen saturation; see Section 6.4.8)		X	X	X	X	X	X		
Weight		X	X	X	X	X		X	
Electrocardiogram (see Section 6.4.7)[e]		X[e]	X[e]			X[e]			
Adverse event/serious adverse event assessment (see Section 6.4.3)	X[f]	X	X	X	X	X	X		
Concomitant medications		X	X	X	X	X	X		
Palliative radiotherapy			As clinically indicated (see Section 5.1) →						
World Health Organisation performance status		X	X	X	X	X		X	
Serum chemistry[g]		X	X	X	X	X	X		

Table 5 Schedule of study procedures for the MEDI4736+tremelimumab arm in Sub-study B: Screening and Treatment Period (up to 50 weeks, maximum of 22 doses of MEDI4736 and 4 doses of tremelimumab. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**							
		Screening	**Randomisation**				**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**85**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12**	**16, 18, 20, 22, 24, etc**	**16, 20, 24, 28, 32, etc**	**16, 24, 32, 40 and 48**
				(±3 days[b])					**(±7 days)**
Amylase, lipase (where available)[g]		X	X	X	X	X		X	
Thyroid function tests (TSH and T3 and T4) (see Section 6.4.9)		X	X	X	X	X		X	
Haematology[g]		X	X	X	X	X	X		
Urinalysis[h]		X	X	X	X	X		X	
Coagulation parameters[i]		X		As clinically indicated →					
Pharmacokinetic MEDI4736 assessment (see Section 6.6.1)[j]			X (and EOI)		X				X (Weeks 24 [and EOI] and 48 only)
Pharmacokinetic tremelimumab assessment (see Section 6.6.1)[j]			X (and EOI)		X			X (Weeks 24 and 36 only)	
Immunogenicity MEDI4736 assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) (see Section 6.6.2)[j]			X		X				X (Weeks 24 and 48 only)

Table 5 Schedule of study procedures for the MEDI4736+tremelimumab arm in Sub-study B: Screening and Treatment Period (up to 50 weeks, maximum of 22 doses of MEDI4736 and 4 doses of tremelimumab. Last infusion at Week 50)

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**All assessments to be performed pre-infusion unless stated otherwise**							
		Screening	**Randomisation**				**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**
Day	**-42 to -1**	**-28 to -1**	**1[a]**	**29**	**57**	**85**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4**	**8[b]**	**12**	**16, 18, 20, 22, 24, etc**	**16, 20, 24, 28, 32, etc**	**16, 24, 32, 40 and 48**
				(±3 days[b])					**(±7 days)**
Immunogenicity tremelimumab assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) (see Section 6.6.2)[j]			X		X			X (Weeks 24 and 36 only)	
sPD-L1 concentration (to assess target engagement) (see Section 6.7)[j]			X		X			X (Weeks 24 and 36 only)	X (Week 48 only)
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) (see Section 6.7)			X	X		X			
CCI [redacted]			[redacted]		[redacted]				
CCI [redacted]		[redacted]							
Tumour assessment (CT or MRI)[k,l,m]		X			X				X

a Every effort should be made to minimise the time between randomisation and starting treatment. It is recommended that patients commence study treatment as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS/IWRS system) and no later than 48 hours after randomisation.

b Week 8 the allowed window for the tumour assessment is ±7 days.

c CCI [redacted]

d MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg administered once every 4 weeks up to 12 weeks (4 doses) then MEDI4736 10 mg/kg alone administered every 2 weeks for 34 weeks starting at Week 16 (18 doses).

e ECGs: At Screening, digital ECGs should be performed in triplicate with a 2- to 5-minute time lag between each measurement. During treatment, mandatory ECGs are performed on Day 1 and at Week 12; only a single digital ECG measurement is required at these visits. On Day 1 and Week 12, ECGs should be taken 30 to 60 minutes before study drug infusion and at least 1 time point 0 to 3 hours after infusion. ECGs should be performed at other times if clinically indicated.

f For SAEs that occur in the pre-screening period additional information such as medical history may be requested.

g If Screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for urea and electrolytes, full blood count and liver function tests must be available before commencing any infusion with study drug. Gamma glutamyltransferase tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and as clinically indicated. Creatinine clearance, magnesium and uric acid tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1), every 4 weeks until Week 12, and every 2 weeks thereafter. Amylase and lipase are tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1), every 4 weeks thereafter.

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

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

j **PK, ADA and sPD-L1 samples** to be collected at Day 1, Week 8, Week 24, Week 36 and Week 48. **PK samples:** At each collection, patients will have samples drawn separately for each of the 2 components of the combination. On Day 1 and Week 24, samples will be collected before and after infusion. At other visits, only a pre-dose sample is required. Pre-dose samples are drawn within 60 minutes prior to the start of infusion and EOT samples within 10 minutes after end of infusion. Note: PK samples on Day 1 are as follows: 2 samples before infusion of the first drug of the combination (pre-dose); 1 sample at the end of the first drug infusion and 1 sample at the end of the second drug infusion (end-of-infusion samples). At Week 36, a pre-dose sample for tremelimumab and at Week 48 a pre-dose sample for MEDI4736 is drawn before infusion. **ADA samples**: At each collection, 2 samples will be drawn from patients with the exception of Weeks 36 and 48 when 1 sample will be drawn. All samples should be collected pre-dose (ie, within 60 minutes prior to the start of the infusion or the start of infusion of the first drug of combination). **sPD-L1 samples**: At each collection, 1 sample only is drawn from patients. All samples should be collected pre-dose only (ie, within 60 minutes prior to the start of the infusion or the start of infusion of the first drug of combination). NB: If a patient discontinues study treatment before 50 weeks, PK, ADA and sPD-L1 samples must still be collected for tremelimumab at 3 and 6 months after the last dose of tremelimumab (Week 24 and Week 36). .

k RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up. The baseline assessment should be performed within the 28 days prior to randomisation and ideally as close as possible before the start of study treatment. Follow-up assessments will be performed every 8 weeks ± 1 week for the first 48 weeks (relative to the date of randomisation) while on treatment until confirmed objective disease progression per RECIST 1.1. The confirmatory scans should be performed to preferably occur at the next scheduled visit (relative to the date of randomisation) and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomisation). All confirmatory scans should be databased. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 4.3. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug.

l Patients in the MEDI4736+tremelimumab arm who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 4th cycle (Week 16, 4 weeks after the last dose of combination treatment) will continue with the planned treatment for this arm ie, MEDI4736 10 mg/kg Q2W. If the patient experiences radiological PD (according to RECIST 1.1), with or without confirmation, during treatment, retreatment with the combination regimen may begin. Before restarting study drug, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3. To restart study drug the patient must not have received an intervening systemic anti-cancer therapy post discontinuation of study drug. Patients should have a baseline tumour assessment within 28 days prior to restarting study drug, all further scans should occur every 8 weeks ± 1 week (relative to the date of restarting study drug), or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3).

m Patients with confirmed PD during the initial treatment period who continue to receive study drug at the discretion of the investigator (following consultation with the sponsor) can receive study drug for a maximum of 12 months. Retreatment may continue as long as the investigator judges the patient to be gaining clinical benefit. Patients will have scans every 8 weeks ± 1 week (relative to the date of randomisation) until treatment with study drug is stopped, or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST per local practice. It is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3). Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug. Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Note: If a patient has a delay to an infusion of study drug all assessments should be conducted relative to the date of randomisation.

Note: For 'retreatment' patients who go on to have subsequent treatment prior to the final DCO, the same assessments should be done as in the first 12-month treatment period with the exception of the PK, ADA, sPD-L1, and PGx, assessments which do not need to be collected a second time. This includes all assessments listed under 'screening' and 'randomisation' which should be completed again following the decision to re-treat. Additionally, if feasible or clinically indicated, a biopsy at entry to re-treatment may optionally be collected.

ADA Anti-drug antibody; APTT Activated partial thromboplastin time; BP Blood pressure; CR Complete response; CT Computed tomography; ECG Electrocardiogram; EOI End of infusion; FFPE Formalin-fixed paraffin-embedded; hCG Human chorionic gonadotropin; HIV Human immunodeficiency virus; INR International normalised ratio; IVRS/IWRS Interactive voice/web response system; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NSCLC Non-small cell lung cancer; PD Progression of disease; PGx Pharmacogenetic(s); PK Pharmacokinetics; PR Partial response; RECIST Response Evaluation Criteria In Solid Tumours; SD Stable disease; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

Table 6 Follow-up for patients who have completed the treatment period for MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab and achieved disease control and patients who have discontinued study drug due to toxicity or a reason other than confirmed progression of disease

Evaluation	Time Since Last Dose on MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)[f]
	30	2	3	4	6	8	10	
Patient questionnaires (patient reported outcomes) and health resource use	For patients who **achieve disease control following 12 months/48 weeks of treatment,** patient questionnaires and information relating to health resource use should be completed every 12 weeks relative to the date of **randomisation** until confirmed PD by RECIST 1.1 by investigational site review. For patients who **discontinue study drug due to toxicity or a reason other than confirmed PD**, patient questionnaires and information relating to health resource use should be completed relative to the date of **randomisation** as follows: every 8 weeks for the first 48 weeks (per Table 3, Table 4 or Table 5), then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review.							
Physical examination	X							
Vital signs (BP, pulse, respiratory rate, temperature, oxygen saturation)	X							
Weight	X							
Adverse event/serious adverse event assessment (see Section 6.4.3)	X	X	X					
Concomitant medications	X							
Palliative radiotherapy	As clinically indicated (see Section 5.1) →							
World Health Organisation performance status[a]	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]
Subsequent anti-cancer therapy[a]	X	X	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Haematology	X	X	X	X				X
Serum chemistry	X	X	X					

Table 6 Follow-up for patients who have completed the treatment period for MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab and achieved disease control and patients who have discontinued study drug due to toxicity or a reason other than confirmed progression of disease

Evaluation	Time Since Last Dose on MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)[f]
	30	2	3	4	6	8	10	
Amylase, lipase (where available)	X	X	X					
Thyroid function tests (TSH, and T3 and T4)	X							
Coagulation parameters[b]	As clinically indicated →							
Urinalysis	As clinically indicated →							
Pharmacokinetic MEDI4736 assessment (MEDI4736+*tremelimumab and* MEDI4736 *monotherapy arms)*[c]			X					
Pharmacokinetic tremelimumab assessment *(*MEDI4736+*tremelimumab and tremelimumab monotherapy arms)*[c]			X					
Immunogenicity MEDI4736 assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) (MEDI4736+*tremelimumab and* MEDI4736 *monotherapy arms)*[c]			X		X			
Immunogenicity tremelimumab assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) *(*MEDI4736+*tremelimumab and tremelimumab monotherapy arms)*[c]			X		X			
sPD-L1 concentration (to assess target engagement)[c]			X					
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation)	X							

Table 6 Follow-up for patients who have completed the treatment period for MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab and achieved disease control and patients who have discontinued study drug due to toxicity or a reason other than confirmed progression of disease

Evaluation	Time Since Last Dose on MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)[f]
	30	2	3	4	6	8	10	
Tumour assessment (CT or MRI)[d,e]	For patients who **achieve disease control following 12 months/48 weeks of treatment,** tumour assessments should be performed every 12 weeks ± 1 week relative to the date of **randomisation** until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 3, Table 4 or Table 5 for timings of confirmatory scans. For patients who **discontinue study drug due to toxicity or a reason other than confirmed PD**, tumour assessments should be performed relative to the date of **randomisation** as follows: every 8 weeks ± 1 week for the first 48 weeks (per Table 3, Table 4 or Table 5), then every 12 weeks ± 1 week until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 3, Table 4 or Table 5 for timings of confirmatory scans. Upon confirmed radiological PD (by RECIST), scans should be conducted according to local standard clinical practice until a new treatment is started (these scans are optional).							

a World Health Organisation 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, please provide World Health Organisation performance status when information on subsequent anti-cancer therapy is provided, where possible.

b Coagulation tests: prothrombin time, APTT and INR will be performed if clinically indicated.

c **PK and ADA**: At 3 months after the last dose of treatment (and again at 6 months for ADA), 2 samples are drawn from those in the MEDI4736+tremelimumab arm and 1 sample from each of the monotherapy arms. **sPD-L1**: At 3 months after the last dose of treatment, 1 sample is drawn from those in each of the 3 treatment arms. NB: If a patient discontinues the MEDI4736+tremelimumab arm, PK, ADA and sPD-L1 samples must still be collected for tremelimumab at 3 and 6 months after the last dose of tremelimumab (Week 24 and Week 36).

d RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy may be imaged based on signs and symptoms of individual patients. Following the final DCO, patients continuing on the study who remain potentially eligible for future re-treatment with MEDI4736 and/or tremelimumab should receive scans/RECIST and other assessments as per investigator's judgment and local standard of care, but in such way that will allow confirmation of re-treatment eligibility criteria per Section 4.3.

e If the patient experiences PD (according to RECIST 1.1), with or without confirmation, during the follow-up phase, retreatment with the initial dosing regimen may begin. Patients can only begin retreatment once, and may continue as long as the investigator judges the patient to be gaining clinical benefit. Before restarting study drug, the investigator should ensure that patients do not have any significant, unacceptable or irreversible toxicities that would indicate continuing treatment will not further benefit the patient. The patient must continue to meet those inclusion and exclusion criteria that are relevant to retreatment as specified in Section 4.3. To restart study drug the patient must not have received an intervening systemic anti-cancer therapy post-discontinuation of study drug. Patients should have a baseline tumour assessment within 28 days prior to restarting study drug, all further scans should occur every 8 weeks ± 1 week (relative to the date of restarting study drug), or, if they continue to receive re-treatment after the final DCO, patients should receive scans/RECIST per local practice. It is recommended that the patients continue the scheduled

site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3).

f Patients on survival follow-up at the time of final DCO will be considered completed from the study and followed per local standard of care.

ADA Anti-drug antibody; APTT Activated partial thromboplastin time; BP Blood pressure; CT Computed tomography; INR International normalised ratio; MRI Magnetic resonance imaging; PD Progression of disease; RECIST Response Evaluation Criteria In Solid Tumours; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

Table 7 Follow-up for patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab due to confirmed progression of disease

Evaluation	Time Since Last Dose on MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)
	30	2	3	4	6	8	10	
Patient questionnaires (patient reported outcomes) [redacted]	For patients who **continue on study drug after confirmed progression** at the investigator's discretion (following consultation with the sponsor), patient questionnaires [redacted] should be completed relative to the date of **randomisation** per Table 3, Table 4 or Table 5until treatment with study drug is stopped. For patients who **discontinue study drug following confirmed progression**, patient questionnaires [redacted] should be completed at the **Day 30 assessment and at Month 3** after confirmed progression, in line with clinic assessments. Questionnaires should be administered before any clinical assessment at these visits.							
Physical examination	X							
Vital signs (BP, pulse, respiratory rate, temperature, oxygen saturation)	X							
Weight	X							
Adverse event/serious adverse event assessment (see Section 6.4.3)	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated (see Section 5.1) →							
World Health Organisation performance status[a]	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]
Subsequent anti-cancer therapy[a]	X	X	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Haematology	X	X	X					
Serum chemistry	X	X	X					
Amylase, lipase (where available)	X	X	X					

Table 7 Follow-up for patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab due to confirmed progression of disease

Evaluation	Time Since Last Dose on MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)
	30	2	3	4	6	8	10	
Thyroid function tests (TSH, and T3 and T4)	X							
Coagulation parameters[b]	As clinically indicated →							
Urinalysis	As clinically indicated →							
Pharmacokinetic MEDI4736 assessment (MEDI4736+*tremelimumab and* MEDI4736 *monotherapy arms)*[c]			X					
Pharmacokinetic tremelimumab assessment *(*MEDI4736+*tremelimumab and tremelimumab monotherapy arms)*[c]			X					
Immunogenicity MEDI4736 assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) (MEDI4736+*tremelimumab and* MEDI4736 *monotherapy arms)*[c]			X					
Immunogenicity tremelimumab assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) *(*MEDI4736+*tremelimumab and tremelimumab monotherapy arms)*[c]			X					
sPD-L1 concentration (to assess target engagement)[c]			X					
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation)	X							

Table 7 Follow-up for patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab due to confirmed progression of disease

Evaluation	Time Since Last Dose on MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)
	30	2	3	4	6	8	10	
Tumour biopsy	A tumour biopsy upon evidence of PD should be performed according to institutional practice. It is accepted that the biopsy procedure should be technically feasible and not associated with unacceptable clinical risk (see Section 6.7)							
Time to second progression	For patients who **continue on study drug post confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of **randomisation** per Table 3, Table 4 or Table 5 until study drug is stopped. Patients who **discontinue study drug following confirmed progression**, will be assessed **every 12 weeks** for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death.							
Tumour assessment (CT or MRI)	For patients who **continue on study drug after confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of randomisation per Table 3, Table 4 or Table 5 until study drug is stopped. For patients who **discontinue study drug following confirmed progression**, **scans should be conducted according to local clinical practice** until a new treatment is started (these scans are optional).							

a World Health Organisation 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, please provide World Health Organisation performance status when information on subsequent anti-cancer therapy is provided, where possible.
b Coagulation tests: prothrombin time, APPT and INR will be performed if clinically indicated.
c **PK and ADA**: At 3 months after the last dose of treatment, 2 samples are drawn from those in the MEDI4736+tremelimumab arm and 1 sample from each of the monotherapy arms. **sPD-L1**: At 3 months after the last dose of treatment, 1 sample is drawn from those in each of the 3 treatment arms. NB: If a patient discontinues the MEDI4736+tremelimumab arm, PK, ADA and sPD-L1 samples must still be collected for tremelimumab at 3 and 6 months after the last dose of tremelimumab (Week 24 and Week 36).

ADA Anti-drug antibody; APTT Activated partial thromboplastin time; BP Blood pressure; CT Computed tomography; INR International normalised ratio; MRI Magnetic resonance imaging; PD Progression of disease; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

Table 8 Schedule of study procedures for patients treated with vinorelbine or gemcitabine in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**All assessments to be performed pre-infusion unless stated otherwise**					
				Cycle X Every 4 weeks				**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**	**Day 1**	**Day 8**	**Day 15**	**Day 22 (vinorelbine only)**	**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, etc**	**1, 5, 9, etc**	**2, 6, 10, etc**	**3, 7, 11, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				---------- (±3 days) ----------				**------- (±7 days) ------**	
Written pre-screening informed consent/assignment of patient identification number (Section 6.2)	X								
Preliminary eligibility fulfilment (investigator's opinion)	X								
Demography and history of tobacco and alcohol use	X								
Previous treatments for NSCLC	X								
Archival (>3 years) FFPE tumour tissue sample for PD-L1 assay (optional) (see Section 6.7)	X								
Newly acquired or archival (≤3 years) formalin-fixed tumour biopsy for PD-L1 assay (mandatory) (see Section 6.7)	X								
Written sub-study informed consent (Note: Patients are required to re-consent to continue study drug when treated through progression [See Section 8.4])		X							
Formal verification of eligibility criteria		X	X						
Randomisation (see Section 5.2)			X						

Table 8 Schedule of study procedures for patients treated with vinorelbine or gemcitabine in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**All assessments to be performed pre-infusion unless stated otherwise**					
				Cycle X Every 4 weeks				**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**	**Day 1**	**Day 8**	**Day 15**	**Day 22 (vinorelbine only)**	**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, etc**	**1, 5, 9, etc**	**2, 6, 10, etc**	**3, 7, 11, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				---------- (±3 days) ----------				------- (±7 days) ------	
Patient questionnaires (patient reported outcomes) (see Section 6.5)[b]		X	X	X				X	
CCI [redacted]			[redacted]	[redacted]					
CCI [redacted]						[redacted]	[redacted]		
Medical and surgical history		X							
Hepatitis B and C; HIV		X							
Height		X							
Urine hCG or serum βhCG		X	X						
Kit assignment and chemotherapy administration			X	X	X	X	X		
Physical examination		X	X	X					
Vital signs (at the beginning and end of each infusion where possible)		X	X	X	X	X	X		
Weight		X	X	X					
Electrocardiogram (see Section 6.4.7)[d]		X							
AE/SAE assessment (see Section 6.4.3)	X	X	X	X	X	X	X		

Table 8 Schedule of study procedures for patients treated with vinorelbine or gemcitabine in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**All assessments to be performed pre-infusion unless stated otherwise**					
				Cycle X Every 4 weeks				**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**	**Day 1**	**Day 8**	**Day 15**	**Day 22 (vinorelbine only)**	**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, etc**	**1, 5, 9, etc**	**2, 6, 10, etc**	**3, 7, 11, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				---------- (±3 days) ----------				**------- (±7 days) ------**	
Concomitant medications		X	X	X	X	X	X		
Palliative radiotherapy			→ As clinically indicated (see Section 5.1) →						
WHO performance status		X	X	X					
Serum chemistry[e]		X	X	X		X			
Amylase, lipase (where available)[e]		X	X				X		
Haematology[e]		X	X	X	X	X	X		
Urinalysis		X	X	X					
Coagulation parameters[f]		X							
Thyroid function tests (TSH and T3 and T4) (see Section 6.4.9)		X							
sPD-L1 concentration (see Section 6.7)[g]			X	X (C3 only)				X (Week 24 only)	
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) (see Section 6.7)[g]			X	X (C2 and C4 only)					

Table 8 Schedule of study procedures for patients treated with vinorelbine or gemcitabine in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**All assessments to be performed pre-infusion unless stated otherwise**					
				Cycle X Every 4 weeks				**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**	**Day 1**	**Day 8**	**Day 15**	**Day 22 (vinorelbine only)**	**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, etc**	**1, 5, 9, etc**	**2, 6, 10, etc**	**3, 7, 11, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				---------- (±3 days) ----------				------- (±7 days) ------	
CCI [redacted]			[redacted]	[redacted]				[redacted]	
CCI [redacted]		[redacted]							
Tumour assessment (CT or MRI)[h]		X						X	

a Every effort should be made to minimise the time between randomisation and starting treatment. It is recommended that patients commence study treatment as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS/IWRS system) and no later than 48 hours after randomisation.

b Patient questionnaires to be completed at Week 1 (Day 1 [Randomisation]), Week 4 (Day 29) and Week 8 (Day 57) and then every 8 weeks for the first 48 weeks then every 12 weeks until confirmed objective disease progression per RECIST 1.1. CCI [redacted]

c CCI [redacted]

d Digital electrocardiograms should be performed at Screening in triplicate with a 2- to 5-minute time lag between each measurement.

e If Screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for urea and electrolytes, full blood count and liver function tests must be available before commencing any infusion with vinorelbine or gemcitabine. Gamma glutamyltransferase tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and as clinically indicated. Creatinine clearance, magnesium, amylase, lipase, and uric acid tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and every 4 weeks thereafter.

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

g **sPD-L1**: Blood samples are collected pre-dose on Day 1, Week 8 and Week 24 only. CCI [redacted]

h RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients. The baseline assessment should be performed within the 28 days prior to randomisation and ideally as close as possible before the start of study treatment. Follow-up assessments will be performed every 8 weeks ± 1 week for the first 48 weeks (relative to the date of randomisation) and then every 12 weeks thereafter until confirmed objective disease progression per RECIST 1.1. A confirmatory scan is required following the initial demonstration of PD. In the Standard of Care arm, it is at the investigator's discretion if a patient with uncertain PD continues treatment until PD is confirmed; however, a confirmatory scan is required for all patients in the Standard of Care arm even if a subsequent treatment is started. The confirmatory scans should be performed to preferably occur at the next scheduled visit (relative to the date of randomisation) and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomisation). All confirmatory scans should be databased. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 4.3.

Note: If a patient has a delay to an infusion of study treatment all assessments should be conducted relative to the date of randomisation.

AE Adverse event; APTT Activated partial thromboplastin time; C Cycle; CT Computed tomography; FFPE Formalin-fixed paraffin-embedded; hCG Human chorionic gonadotropin; HIV Human immunodeficiency virus; INR International normalised ratio; IVRS/IWRS Interactive Voice/Web Response System; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NSCLC Non-small cell lung cancer; PD Progression of disease; PGx Pharmacogenetic(s); RECIST Response Evaluation Criteria In Solid Tumours; SAE Serious adverse event; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; WHO World Health Organisation.

Table 9 Schedule of study procedures for patients treated with erlotinib in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**Cycle X, Day 1 Every 4 weeks**	**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, 12, 16, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				------- (±2 days) ------	**---------- (±7 days) ----------**	
Written pre-screening informed consent/assignment of patient identification number (Section 6.2)	X					
Preliminary eligibility fulfilment (investigator's opinion)	X					
Demography and history of tobacco and alcohol use	X					
Previous treatments for NSCLC	X					
Archival (>3 years) FFPE tumour tissue sample for PD-L1 assay (optional) (see Section 6.7)	X					
Newly acquired or archival (≤3 years) formalin-fixed tumour biopsy for PD-L1 assay (mandatory) (see Section 6.7)	X					
Written sub-study informed consent (Note: Patients are required to re-consent to continue study drug when treated through progression [See Section 8.4])		X				
Formal verification of eligibility criteria		X	X			
Randomisation (see Section 5.2)			X			

Table 9 Schedule of study procedures for patients treated with erlotinib in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**Cycle X, Day 1 Every 4 weeks**	**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**	**Day 1 of the week**		
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, 12, 16, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				------- (±2 days) ------	**---------- (±7 days) ----------**	
Patient questionnaires (patient reported outcomes) (see Section 6.5)[b]		X	X	X	X	
CCI [redacted]			[redacted]	[redacted]		
[redacted]				CCI [redacted]		
Medical and surgical history		X				
Hepatitis B and C; HIV		X				
Height		X				
Urine hCG or serum βhCG		X	X			
Erlotinib dispensing			X	X		
Physical examination		X	X	X		
Vital signs		X	X	X		
Weight		X	X	X		
Electrocardiogram (see Section 6.4.7)[d]		X				
AE/SAE assessment (see Section 6.4.3)	X	X	X	X		
Concomitant medications		X	X	X		
WHO performance status		X	X	X		

Table 9 Schedule of study procedures for patients treated with erlotinib in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**Cycle X, Day 1 Every 4 weeks**	**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, 12, 16, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				------- (±2 days) ------	**---------- (±7 days) ----------**	
Palliative radiotherapy				As clinically indicated (see Section 5.1) →		
Serum chemistry[e]		X	X	X		
Amylase, lipase (where available)[e]		X	X	X		
Haematology[e]		X	X	X		
Urinalysis		X	X	X		
Coagulation parameters[f]		X				
Thyroid function tests (TSH and T3 and T4) (see Section 6.4.9)		X				
sPD-L1 concentration (see Section 6.7)[g]			X	X (C3 only)	X (Week 24 only)	
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) (see Section 6.7)[g]			X	X (C2 and C4 only)		
CCI [redacted]			[redacted]	[redacted]	[redacted]	
CCI [redacted]		[redacted]				

Table 9 Schedule of study procedures for patients treated with erlotinib in the Standard of Care arm (a cycle=4 weeks): Screening and Treatment Period

Visit (Assessments to be performed at the times stipulated and as clinically required in the management of the patient.)	**Pre-screening for PD-L1 status ONLY**	**Screening**	**Randomisation**	**Cycle X, Day 1 Every 4 weeks**	**Every 8 weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**Day 1[a]**		**Day 1 of the week**	
Week	**-6 to -1**	**-4 to -1**	**0**	**4, 8, 12, 16, etc**	**8, 16, 24, 32, 40, 48, etc**	**16, 28, 40, 52, etc**
				------- (±2 days) ------	**---------- (±7 days) ----------**	
Tumour assessment (CT or MRI)[h]		X			X	

a Every effort should be made to minimise the time between randomisation and starting treatment. It is recommended that patients commence study treatment as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS/IWRS system) and no later than 48 hours after randomisation.

b Patient questionnaires to be completed at Week 1 (Day 1 [Randomisation]), Week 4 (Day 29) and Week 8 (Day 57) and then every 8 weeks for the first 48 weeks then every 12 weeks until confirmed objective disease progression per RECIST 1.1. CCI [redacted]

c CCI [redacted]

d Digital electrocardiograms should be performed at Screening in triplicate with a 2- to 5-minute time lag between each measurement.

e If Screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Gamma glutamyltransferase tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and as clinically indicated. Creatinine clearance, magnesium, amylase, lipase, and uric acid tested at Screening, Day 1 (if screening laboratory assessments are not performed within 3 days prior to Day 1) and every 4 weeks thereafter.

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

g **sPD-L1**: Blood samples are collected pre-dose on Day 1, Week 8 and Week 24 only. CCI [redacted]

h RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients. The baseline assessment should be performed within the 28 days prior to randomisation and ideally as close as possible before the start of study treatment. Follow-up assessments will be performed (relative to the date of randomisation) every 8 weeks ± 1 week for the first 48 weeks and then every 12 weeks thereafter until confirmed objective disease progression per RECIST 1.1. A confirmatory scan is required following the initial demonstration of PD. In the Standard of Care arm, it is at the investigator's discretion if a patient with uncertain PD continues treatment until PD is confirmed; however, a confirmatory scan is required for all patients in the Standard of Care arm even if a subsequent treatment is started. The confirmatory scans should be performed to preferably occur at the next scheduled visit (relative to the date of randomisation) and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomisation). All confirmatory scans should be databased. For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further

benefit the patient**.** The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 4.3.

AE Adverse event; APTT Activated partial thromboplastin time; C Cycle; CT Computed tomography; FFPE Formalin-fixed paraffin-embedded; hCG Human chorionic gonadotropin; HIV Human immunodeficiency virus; INR International normalised ratio; IVRS/IWRS Interactive Voice/Web Response System; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NSCLC Non-small cell lung cancer; PD Progression of disease; PGx Pharmacogenetic(s); RECIST Response Evaluation Criteria In Solid Tumours; SAE Serious adverse event; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; WHO World Health Organisation.

Table 10 Follow-up for patients in the Standard of Care arm

Evaluation	Time since last dose of Standard of Care treatment							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)
	30	2	3	4	6	8	10	
Patient questionnaires (patient reported outcomes)	For patients who **discontinue study drug due to toxicity or a reason other than confirmed PD**, patient questionnaires and information for health resource use should be completed relative to the date of **randomisation** as follows: every 8 weeks for the first 48 weeks, then every 12 weeks thereafter until confirmed PD by RECIST 1.1 by investigational site review.							
Health resource use instrument	For patients who **discontinue study treatment following confirmed progression**, patient questionnaires and information on health resource use should be completed at the **Day 30 assessment and at Month 3** after confirmed progression, in line with clinic assessments. Questionnaires should be administered before any clinical assessment at these visits.							
Physical examination	X							
Vital signs	X							
Weight	X							
AE/SAE assessment (see Section 6.4.3)	X							
Concomitant medications	X							
Palliative radiotherapy		As clinically indicated (see Section 5.1) →						
World Health Organisation performance status[a]	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Haematology	X							X[b]
Serum chemistry	X							
Amylase, lipase (where available)	X							
Coagulation parameters		As clinically indicated →						

Table 10 Follow-up for patients in the Standard of Care arm

Evaluation	Time since last dose of Standard of Care treatment							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months Thereafter (±2 weeks)
	30	2	3	4	6	8	10	
Urinalysis		As clinically indicated →						
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation)	X							
Tumour biopsy	A tumour biopsy upon evidence of PD should be performed according to institutional practice. It is accepted that the biopsy procedure should be technically feasible and not associated with unacceptable clinical risk (see Section 6.7)							
Tumour assessment (CT or MRI)	For patients who **discontinue study treatment due to toxicity or a reason other than confirmed PD**, tumour assessments should be performed relative to the date of **randomisation** as follows: every 8 weeks ± 1 week for the first 48 weeks, then every 12 weeks thereafter until confirmed PD by RECIST 1.1. Please refer to Table 8 (gemcitabine and vinorelbine) and Table 9 (erlotinib) for timings of confirmatory scans. Upon confirmed PD, scans should be conducted according to local standard clinical practice until a new treatment is started (these scans are optional).							
Time to second progression	Patients who **discontinue study treatment following confirmed progression**, will be assessed every 12 weeks for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death.							

a World Health Organisation 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, please provide World Health Organisation performance status when information on subsequent anti-cancer therapy is provided, where possible.
b Only for patients who have discontinued treatment due to toxicity or a reason other than confirmed PD.
AE Adverse event; CT Computed tomography; MRI Magnetic resonance imaging; PD Progression of disease; RECIST Response Evaluation Criteria In Solid Tumours; SAE Serious adverse event; sPD-L1 Soluble programmed death ligand 1.

3.2 Rationale for study design, doses and control groups

3.2.1 Unmet need and potential role of immunotherapies in NSCLC

Current therapies for advanced NSCLC have poor outcomes and there is still a significant unmet medical need for additional treatment options for use in this patient population. Patients who fail second-line chemotherapy usually have a poor prognosis with median survival of <6 months. The outlook for refractory advanced NSCLC is extremely poor, with response to further systemic therapy of <10% (GLOBOCAN 2008, Hanna et al 2004).

Single agent chemotherapy is an acceptable option for patients who fail first- or second-line systemic treatment. However, the impact on PFS and OS is generally modest; thus, novel and more effective therapeutic strategies are needed. Erlotinib (TARCEVA®), an EGFR inhibitor, also provides a modest improvement in OS in patients who have failed first- or second-line chemotherapy (TARCEVA® prescribing information). In a randomised, placebo-controlled, double-blind trial comparing erlotinib with placebo, patients treated with erlotinib showed OS of 6.7 months versus 4.7 months for placebo (HR: 0.73; 95% CI: 0.61 to 0.86); PFS was 2.3 months for the erlotinib group versus 1.8 months for the placebo group (HR: 0.59; 95% CI: 0.50 to 0.70).

3.2.2 Potential role for MEDI4736 monotherapy (Sub-study A), and MEDI4736+tremelimumab, MEDI4736 monotherapy and tremelimumab monotherapy (Sub-study B) in the treatment of NSCLC

Although clinical experience with MEDI4736 is limited, currently available data from the MEDI4736 FTIH study (Section 1.4.1 and MEDI4736 IB), indicates encouraging response rates and DoR, with a manageable safety profile in patients with a variety of solid malignancies, including patients with NSCLC. These are advanced patients who have failed multiple lines of therapy. These emerging data support the proposed further investigation of MEDI4736 in patients with advanced/metastatic NSCLC who have failed 2 prior lines of therapy in a controlled Phase III setting. Furthermore, data on MEDI4736 presented at ESMO 2014 showed an ORR of 16% in the overall NSCLC patient population and a 25% ORR in the PD-L1-positive subset of patients and an ORR of 10% in the PD-L1-negative subset of patients (Antonia et al 2014 ESMO), consistent with the principle that the selection of patients based on PD-L1 expression within the tumour microenvironment may have merit as a patient enrichment tool. Updated safety and efficacy data from this study was presented at international oncology conferences (Rizvi et al 2015 ASCO). Nonetheless, patients with PD-L1-negative tumours also received benefit from MEDI4736.

Although clinical experience with tremelimumab monotherapy in NSCLC is limited, Study A3671015 suggested a trend in benefit in PFS at 3 months, and some partial responses to treatment, including in a patient who crossed over from the Best Supportive Care arm after PD. The evolved dosing approach of 10 mg/kg Q4W merits further investigation in the NSCLC population. The safety profile using the greater exposure remains manageable.

Although clinical experience with MEDI4736+tremelimumab is limited, currently available data from a Phase Ib study in patients with advanced NSCLC (Section 1.1.5 and

MEDI4736 IB) demonstrate an acceptable and manageable safety and tolerability profile for the combination. Additionally, prior studies combining anti-PD-L1 and anti-CTLA-4 antibodies have suggested that the efficacy of combination blockade is less dependent on PD-L1 expression (Wolchok et al 2013). With the availability of multiple agents targeting the subset of NSCLC patients with PD-L1-positive tumours, the subset of NSCLC patients with PD-L1-negative tumours become a group with a great unmet need and limited therapeutic options. MEDI4736 monotherapy, tremelimumab monotherapy or the combination of MEDI4736+tremelimumab as therapeutic options may fill this gap in NSCLC patients with PD-L1-negative tumours. The totality of evidence supports the proposed investigation of either monotherapy or MEDI4736+tremelimumab in patients with PD-L1 negative advanced/metastatic NSCLC who have failed 2 prior lines of therapy.

3.2.3 Study design rationale

3.2.3.1 MEDI4736 monotherapy dose justification

A MEDI4736 dose of 10 mg/kg Q2W up to a maximum of 12 months is recommended for further development.

The proposed dose of 10 mg/kg Q2W is supported by multiple lines of evidence including: in-vitro data, non-clinical activity, clinical PK/PDx, biomarkers and activity data (ongoing FTIH study). Although clinical activity has been observed at lower doses, no DLTs were observed up to a dose of 10 mg/kg Q2W or 15 mg/kg every 3 weeks. The proposed dosing regimen of 10 mg/kg Q2W is expected to (a) achieve a target median concentration of approximately 100 µg/mL (identified based on pre-clinical and clinical data) (b) account for anticipated variability in PK, PD 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-tumour activity in animal model.

Based on PK/PDx data from the ongoing FTIH study with dose ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks, MEDI4736 exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W dose, suggesting near complete target saturation (membrane bound and soluble PD-L1). The expected mean trough concentration following 3 mg/kg Q2W is approximately 50 µg/mL. The expected half life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral soluble PD-L1 was observed over the dose range studied, consistent with engagement of MEDI4736 with PD-L1. Pharmacokinetic simulations indicate that following a 10 mg/kg Q2W dose of MEDI4736, >90% patients are expected to maintain PK exposure, yielding full target saturation throughout the dosing interval.

Data generated during the dose escalation phase of the FTIH study also suggest that higher doses (ie, 10 mg/kg Q2W) may be associated with better clinical activity while still providing an acceptable safety profile. Dose-related changes in a variety of peripheral biomarkers have been observed over the dose range of 0.1 to 3 mg/kg Q2W. Thus far, a low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to MEDI4736. Overall, a low incidence of ADA has been observed. Of

the 220 patients who received MEDI4736 monotherapy and for whom PK/ADA data were available as of July 2014, 5 were detected to be ADA positive, with an impact on PK/PDx reported in 1 patient. Thus, the clinical activity observed, coupled with the safety profile, translational science correlates and non-clinical data, supports further development with a dose of 10 mg/kg Q2W.

3.2.3.2 Tremelimumab monotherapy dose justification

Please see Section 1.1.4 for more information regarding safety. An extensive programme of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anti-cancer agents to support various cancer indications using different dose schedules. Tremelimumab has been administered as a single-agent treatment to patients participating in 11 sponsored clinical studies, 3 of which are ongoing. In total, more than 1400 patients with a variety of tumour types have been treated with tremelimumab given alone or in combination with other anti-cancer agents in 34 sponsored clinical studies.

Risks with tremelimumab monotherapy are gastrointestinal 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; other gastrointestinal events (ulcerative colitis, dehydration, nausea and vomiting); hepatic events (hepatitis and liver enzyme elevations); pneumonitis and interstitial lung disease; clinical manifestations of pancreatitis; nervous system events (encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness); cytopenias (thrombocytopenia, anaemia and neutropenia); infusion-related reactions, anaphylaxis and allergic reactions; renal events (renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalaemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis); hyperglycaemia and diabetes mellitus; and pyrexia. The mechanism of action for these risks is thought to be immune-mediated and reflective of the pharmacology of tremelimumab.

Complete updated clinical information, including updates on the identified and potential safety risks, efficacy and pharmacokinetic data, can be found in the current version of the tremelimumab IB.

Across the clinical development programme for tremelimumab, and that of the related anti-CTLA-4 antibody ipilimumab, a pattern of efficacy has emerged that appears to be consistent across different tumour types for anti-CTLA-4 agents. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%; however, in patients who respond, the responses are often durable, lasting several months even in patients with aggressive tumours such as refractory metastatic melanoma. In addition, survival benefit was reported even in patients without radiographical regression in their tumour burden.

As discussed in Section 1.3, tremelimumab at a concentration of 30 µg/mL enhanced IL-2 release (in vitro) and showed anti-tumour activity (in vivo), and was consequently identified

as the target concentration. Pharmacokinetic simulations indicate that following a dose of 10 mg/kg Q4W for 6 months, approximately 90% of patients are expected to be above this target level of 30 µg/mL during the induction phase. Tremelimumab at a dose of 10 mg/kg Q4W for 6 months followed by 10 mg/kg every 90 days is expected to yield PK exposures similar to those of the related anti-CTLA-4 mAb ipilimumab, given at a dose of 10 mg/kg every 3 weeks followed by 10 mg/kg every 3 months, the dosing regimen that was tested in the pivotal first-line melanoma trial (Robert et al 2011).

In addition, retrospective analyses of the Phase I and II tremelimumab melanoma studies show an improvement in OS for patients who were able to achieve a higher tremelimumab exposure, as measured by the area under the plasma concentration-time curve. The median OS was significantly longer in the high-AUC group (15.3 months; N=164) versus the low-AUC group (6.0 months; N=163) (based on the median value of AUC [103570 µg•hr/mL]). This difference in OS corresponds to a HR of 0.41; $p<0.001$, and the estimated survival rates in the 2 groups were 59% versus 29% at 1 year and 15.9% versus 1.2% at 2 years.

A dose schedule of 10 mg/kg Q4W for 6 months followed by 10 mg/kg Q12W is the dose and schedule used in tremelimumab studies that have been started since May 2012. Study D4880C00003 is a randomised, double-blind Phase IIb study comparing tremelimumab to placebo in second-or third-line treatment of patients with unresectable pleural or peritoneal malignant mesothelioma. The primary objective of this study is to compare OS between the 2 treatment arms, and secondary objectives include disease control rate, PFS, patient-reported outcomes, ORR, duration of ORR, safety and tolerability, immunogenicity, and PK. In this study, tremelimumab is administered iv at 10 mg/kg Q4W for 7 doses, followed by Q12W. Results from the primary analysis based on 571 randomised patients can be found in the current version of the tremelimumab IB.

It is anticipated that the proposed dose and schedule, which is based on PK as well as PDx measures such as IL-2 release, coupled with the safety profile, and non-clinical data, supports a study evaluating a dose of 10 mg/kg Q4W for 24 weeks followed by 10 mg/kg Q12W for an additional 24 weeks in third- and fourth-line NSCLC patients.

3.2.3.3 Dose justification for the combination of MEDI4736 20 mg/kg IV Q4W with tremelimumab 1 mg/kg IV Q4W for 4 cycles

The dose and schedule of MEDI4736 20 mg/kg and tremelimumab 1 mg/kg Q4W was selected based on PK/PDx, safety and efficacy data from Study D4190C0006. The goal of dose selection was to identify an optimal dose of MEDI4736 and tremelimumab that would result in pharmacologically active doses of both drugs as measured by sustained target suppression (soluble programmed cell death ligand 1 [sPD-L1]) and evidence of increased T-cell proliferation and activation, demonstrate promising efficacy and have an acceptable safety profile.

As of 27 January 2015, a total of 74 patients with advanced non-small cell lung cancer 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 every 2 week (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 PDx values.

In order to reduce the dosing frequency of MEDI4736 to align with the Q4W dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety and efficacy cohorts were narrowed to 15 and 20 mg/kg MEDI4736 Q4W.

Safety data from the 15 and 20 mg/kg MEDI4736 cohorts demonstrated a numerical increase in the frequency of treatment-related AEs and AEs leading to discontinuation of investigational product with increasing doses (>1 mg/kg) of tremelimumab.

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. Complete updated clinical data on the MEDI4736 and tremelimumab combination can be found in the current MEDI4736 IB.

3.2.3.3.1 Rationale for tremelimumab 1 mg/kg Q4W in the combination with MEDI4736

Pre-clinical and clinical data indicate that 1 mg/kg tremelimumab delivered Q4W is a pharmacologically active dose.

Pre-clinical studies of tremelimumab showed significant enhancement of in vitro cytokine release in the SEA super-antigen assay at concentrations ranging from 10 to 30 µg/mL. Pre-clinical models indicate that a trough concentration of approximately 30 µg/mL is associated with anti-tumour activity in-vivo. Available clinical PK data demonstrate that 1 mg/kg Q4W would result in median C_{max} to be approximately 30 µg/mL followed by a decrease in median concentration to approximately 6 µg/mL by the end of dosing interval at steady state.

Monotonic increases in PDx activity with the combination (increased activation/proliferation markers on CD4 and CD8 T-cells in periphery) were observed with increasing doses of tremelimumab (1, 3, 10 mg/kg). There was evidence of augmented PDx activity, most notably CD8 T-cell proliferation as measured by Ki67, relative to MEDI4736 monotherapy even with combination doses containing 1 mg/kg tremelimumab.

Clinical activity of the MEDI4736 and tremelimumab combination did not appear to provide a qualitative change with increasing doses of tremelimumab above 1 mg/kg; however, among

the 10 PD-L1 negative patients who received combination doses containing tremelimumab at 1 mg/kg, objective response was noted in 3 (30%) patients.

3.2.3.3.2 Dose justification for MEDI4736 20 mg/kg Q4W

To maximise MEDI4736 exposure with an acceptable safety profile, the highest dose of 20 mg/kg was selected. Preclinical and clinical data supports a decreased frequency of MEDI4736 dosing at 20 mg/kg IV Q4W.

Preclinical data

A population PK model was developed using monotherapy data from a Phase I study (*doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W;* Fairman et al 2014). This population PK model adequately described monotherapy PK data and was utilised to predict expected PK exposures following 20 mg/kg Q4W dosing regimens (*since none of the monotherapy studies explored Q4W regimens*). Pharmacokinetic simulations indicate that a similar overall exposure as represented by AUC at steady state (AUC_{ss}; 4 weeks) is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens. However, median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (approximately 1.5-fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (approximately 1.25-fold). Based on similarity in overall exposure, use of either 20 mg/kg Q4W or 10 mg/kg Q2W is acceptable.

Clinical data

In addition, limited PK data from Study D4190C00006 was available from the combination cohort: 20 mg/kg Q4W MEDI4736 plus 1 or 3 mg/kg Q4W tremelimumab. The observed MEDI4736 PK data from this combination study were well in line with the predicted monotherapy PK data. This indicates no PK interaction between these 2 agents and supports that combination PK data adequately represent the monotherapy data from the 20 mg/kg Q4W cohort.

Furthermore, in Study 1108, as of 02 February 2015, there are 6 patients dosed in the monotherapy MEDI4736 cohort of 20 mg/kg IV Q4W. All patients have received at least 1 dose. One patient has reported 2 unrelated AEs (Grade 1 diarrhoea [recovered] and Grade 2 abdominal pain [ongoing]). No AEs have been reported for the other 5 patients. Updated safety data for this study is found in the latest MEDI4736 IB.

In conclusion, MEDI4736 20 mg/kg Q4W demonstrated comparable overall exposure to MEDI4736 10 mg/kg Q2W and does not demonstrate PK interactions when dosed with tremelimumab, and has manageable toxicity.

3.2.3.3.3 Justification for 4 cycles of the combination regimen:

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), show 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 every 2 weeks 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 – 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, 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 are 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 or anti PDL1 such as MEDI4736 or the combination of the 2.

Similarly, the combination regimen will be administered for 4 doses. Once the combination cycles end, patients will revert to a MEDI4736 10 mg/kg Q2W schedule.

Therefore, there is precedent to utilise MEDI4736 20 mg/kg Q4W in combination with tremelimumab 1 mg/kg Q4W for 4 cycles, then to proceed with MEDI4736 10 mg/kg Q2W monotherapy for the remainder of the 12 month treatment period.

3.2.3.3.4 Conclusion:

In conclusion, the combination of 20 mg/kg MEDI4736 and 1 mg/kg tremelimumab Q4W for 4 doses was chosen based on PK/PDx data and based on the balance of safety and clinical activity. This is justified based on the following:

- Pharmacokinetic data following treatment with MEDI4736 monotherapy or in combination with tremelimumab demonstrate equivalence in exposure of MEDI4736 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when MEDI4736 and tremelimumab are dosed together,
- Following MEDI4736 in combination with tremelimumab, complete sPD-L1 suppression (surrogate for PD-L1 targeting) was observed in almost all patients over the dose range of 3 to 20 mg/kg MEDI4736 Q4W or Q2W.
- Use of tremelimumab 1 mg/kg Q4W provides the optimal balance between safety and clinical activity when utilised in combination with MEDI4736 20 mg/kg Q4W.

3.2.3.4 Justification for Standard of Care as a comparator

Several drugs are used for the treatment third-line treatment for NSCLC, and patients entering this study may have received a variety of prior regimens. Therefore, the comparator has been chosen as Standard of Care as this would depend upon treatments the patient has received as well as upon availability of drugs per centre. The Standard of Care used at study sites will be in-line with local treatment practices in the relevant country/region. The choice of Standard of Care has been restricted to an EGFR TKI (erlotinib), gemcitabine or vinorelbine. Patients in the comparator arm will receive study treatment until progression per standard practice. Patients will continue to receive Standard of Care until confirmed objective disease progression if, in the opinion of the investigator, the patient is not experiencing significant toxicity and it does not contravene local practice. Patients will attend scheduled visits until discontinuation of the last study treatment.

An open label design was needed for this study due to the different schedules and methods of administration of treatments in the study (iv and oral).

3.2.3.5 Rationale for patient selection (based on biomarkers)

Predictive biomarkers and rationale for assigning patients to either Sub-study A or Sub-study B within Study D4191C00004 based on tumoural PD-L1 expression

Sub-study A (MEDI4736 monotherapy)

Published experience with the anti-PD-1/PD-L1 class suggests that it might be beneficial to enrich the patient population by selecting those patients who are considered to be most likely to respond to therapy. At the time of the initial writing of this protocol, no assay has been established/validated and no single approach has proven accurate for patient enrichment for immune-mediated therapies. However, independent data from multiple sources using different assays and scoring methods suggest that PD-L1 expression on tumour cells and/or tumour-infiltrating cells may be associated with greater clinical benefit. For example, data presented by Roche at the Annual Meeting of the ASCO 2013 (Powderly et al 2013) suggested that PD-L1 expression on infiltrating lymphocytes in NSCLC, melanoma, and renal cell carcinoma patient cohorts is associated with greater clinical benefit from anti-PD-L1 treatment. Using a proprietary assay for PD-L1 immunohistochemistry, they found a 36% ORR in patients who had PD-L1-positive tumours with 50% of patients with PD-L1-positive tumours having SD and 33% having PRs. In contrast, in patients with PD-L1-negative tumours, they found only a 13% ORR with 28% of patients having SD and 13% having PRs.

Similarly, in data presented by Grosso and colleagues at the Annual Meeting of ASCO (Grosso et al 2013), PD-L1 staining, when assessed using a different method and scoring algorithm, appeared to be associated with greater clinical benefit in patients with metastatic melanoma treated with nivolumab (anti-PD-1). They found a 44% ORR in patients with PD-L1-positive tumours versus a 17% ORR in patients with PD-L1-negative tumours. Additionally, in their studies, patients with tumours that were PD-L1-positive had a higher PFS (9.1 versus 2.0 months) and OS than patients with PD-L1-negative tumours (21 versus 12 months). Also, in a data set presented by Garon et al at the World Conference on Lung

Cancer (Garon et al 2013), analysis of the relationship between PD-L1 expression status and response rates in a cohort of patients with NSCLC indicated that tumour samples displaying high levels of expression (according to their assay criteria) were associated with response rates of 67% (6/9) per irRC and 57% (4/7) per RECIST. In contrast, tumour samples expressing zero/low levels of PD-L1 were associated with response rates of 4% (1/24) per irRC and 9% (2/22) per RECIST. Similarly, data on MEDI4736 presented at ESMO 2014 showed an ORR of 16% in the overall NSCLC patient population, a 25% ORR in the PD-L1-positive subset of patients and a 10% ORR in the PD-L1-negative subset of patients (Antonia et al 2014 ESMO). Updated efficacy data from MEDI4736 was presented at international oncology conferences (Rizvi et al 2015 ASCO) and is described in detail in the latest MEDI4736 IB.

Therefore, it appears that selection of patients based upon tumour PD-L1 expression may improve the probability and/or quality of response to PD-1 pathway targeting agents and, therefore, may have merit as a patient enrichment tool.

Sub-study B (MEDI4736+tremelimumab, MEDI4736 monotherapy and tremelimumab monotherapy)

While NSCLC patients with PD-L1-positive tumours may receive greater benefit from anti-PD-L1 therapies, a few NSCLC patients with PD-L1-negative tumours have had responses on the FTIH study. Therefore, due to the limited standard of care options available to these patients, studying the MEDI4736 monotherapy is warranted

Although clinical experience with tremelimumab monotherapy in NSCLC is limited, Study A3671015 suggested a trend in benefit in PFS at 3 months, and some partial responses to treatment, including in a patient who crossed over from the Best Supportive Care arm after PD. The evolved dosing approach of 10 mg/kg Q4W merits further investigation in the NSCLC population. The safety profile using the greater exposure remains manageable.

Non-clinical and clinical research suggests that combinations of IMT agents may generate superior anti-tumour activity, compared to single-agent immunotherapy, which may translate into higher and more durable rates of response. As a result, concurrent targeting of immunologic checkpoints with multiple inhibitory/stimulatory molecules may enhance efficacy.

A study investigating the combination of a PD-1 inhibitor (nivolumab) and a CTLA-4 inhibitor (ipilimumab) in patients with melanoma suggested that the combination of CTLA-4 and PD-1 blockade may be active regardless of tumoural PD-L1 expression (Wolchok et al 2013).

With the availability of multiple agents targeting the subset of NSCLC patients with PD-L1-positive tumours, the subset of NSCLC patients with PD-L1-negative tumours become a group with a great unmet need and limited therapeutic options. MEDI4736 monotherapy, tremelimumab monotherapy or the combination of MEDI4736+tremelimumab as therapeutic options regardless of tumoural PD-L1 represents opportunities that may fill this gap.

Emerging safety data from these early studies exploring the combination of immune checkpoint inhibitors indicate an increased frequency and/or severity of some toxicities, such as immune-related toxicities, which are manageable based on immune-related toxicity management guidelines.

PD-L1 testing will be completed on either a recent tissue biopsy (preferred) or an archival sample prior to sub-study assignment (details will be provided in the Investigator's Laboratory Manual). The Ventana PD-L1 immunohistochemistry assay will be used to determine PD-L1 status in this study. Results from other assays will not be accepted in lieu of results obtained from the Ventana test.

In patients where both archived (≤3 years) and newly acquired samples are available, both samples will be analysed to gain understanding about the relationship between these samples, co-evolution of a patient's tumour and immune system, and to help determine which sample type may have the greatest utility for predicting response to therapy. If both samples are submitted prior to sub-study assignment, the PD-L1 result from the most recently acquired sample will always take precedence in sub-study assignment unless such sample is unevaluable or unavailable. In the event that a sample is unevaluable or unavailable, the other sample can be used for sub-study assignment. Optional, additional archived samples >3 years will be used for exploratory analysis only and not for PD-L1 determination and sub-study assignment.

Patient selection based on EGFR TK activating mutations and ALK rearrangements

Patients with known EGFR TK activating mutations and ALK rearrangements are not eligible for this study. Patients negative for EGFR TK activating mutations and ALK rearrangements are likely to have a poorer prognosis and reduced survival than patients with positive EGFR TK mutation status or ALK fusion status. There are clear biological and treatment outcome differences between patients with NSCLC with EGFR/ALK positive tumours and those patients with EGFR/ALK negative tumours. It is considered that patients with "actionable mutations", which have subsequently received the appropriate molecularly targeted therapy (ie, an EGFR or ALK TKI) as part of their prior courses of treatment, comprise a subgroup of NSCLC patients with a different clinical course and prognosis distinct from those with proven EGFR/ALK negative tumours. Therefore, assessing efficacy and safety separately in patients with EGFR/ALK negative tumours is a reasonable choice based on the natural history of the disease and response to therapy, which ultimately impacts prognosis and OS.

Investigators should follow their local clinical practice guidelines for the testing of EGFR and ALK prior to considering a patient for the study. It is recommended that an EGFR mutation status should be systematically analyzed - with sequencing as a standard - in patients with advanced NSCLC with a non-squamous histology. Any patient with a tumour bearing an activating (sensitizing) EGFR mutation should be considered for an EGFR TKI in any line of therapy, if not received previously. ALK activity can be efficiently targeted by the TKI crizotinib, and routine testing for ALK rearrangements should be considered where this drug is available. In the presence of an ALK rearrangement, second third-line treatment with crizotinib should be considered if not received as part of first-line therapy.

3.2.3.6 Rationale for study endpoints (efficacy)

The primary aim of this study is to determine the efficacy of MEDI4736 (10 mg/kg Q2W via iv infusion) or MEDI4736+tremelimumab (MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg Q4W iv up to 12 weeks [4 doses] then MEDI4736 10 mg/kg Q2W iv, starting at Week 16, for 34 weeks [18 doses]) compared with Standard of Care in terms of OS and PFS. Testing for improvements in OS provides a non-biased assessment of direct clinical benefit to a patient (FDA Guidance 2011). Progression free survival may serve as a surrogate endpoint for OS when differences between treatment groups are of sufficient magnitude and clinically important (FDA Guidance 2011, Pazdur 2008).

Anti-tumour activity will be assessed according to RECIST v1.1 guidelines. The co-primary analyses of PFS and sensitivity analyses (Sub-study B) will be based on programmatically-derived PFS based upon investigator assessment.

This is because the response to immunotherapy may differ from typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009):

1. Response to immunotherapy may be delayed

2. Response to immunotherapy may occur after PD by conventional criteria

3. The appearance of new lesions may not represent PD with immunotherapy

4. SD while on immunotherapy may be durable and represent clinical benefit.

To account for these differences, RECIST will be modified so that radiological PD must be confirmed no earlier than 4 weeks after the prior assessment of PD in the absence of clinically significant deterioration. Treatment will continue between the initial assessment of progression and confirmation for progression. In addition, patients may continue to receive study treatment beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment. In the absence of clinically significant deterioration, RECIST with such modifications may discourage the early discontinuation of study treatment and provide a more complete evaluation of its anti-tumour activity than would be seen with conventional response criteria. However, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

The co-primary endpoints for each sub-study are OS and PFS using RECIST v1.1 criteria, and each sub-study has been sized to characterise the PFS and OS benefit of MEDI4736 10 mg/kg Q2W (in the PD-L1-positive population) and MEDI4736 20 mg/kg plus tremelimumab

1 mg/kg Q4W up to 12 weeks (4 doses) then MEDI4736 10 mg/kg Q2W, starting at Week 16, for 34 weeks (18 doses) (in the PD-L1-negative population). Alpha will be controlled across all hypotheses in each sub-study.

3.2.3.7 Rationale for study endpoints (other exploratory endpoints)

CCI [redacted]

CCI [redacted]

CCI [redacted]

4. PATIENT SELECTION CRITERIA

The patient population should be selected without bias. Investigator(s) should keep a record (patient screening log) of patients who entered Pre-screening.

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

4.1 Inclusion criteria

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

1. Provision of signed, written and dated informed consent prior to any study specific procedures

2. Male or female aged 18 years or older

3. Patients must have EITHER

   - Histologically- or cytologically-documented NSCLC who present with Stage IIIB/ Stage IV disease (according to Version 7 of the IASLC Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology]), OR

   - Recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease)

4. Patients must have received at least 2 prior systemic treatment regimens for NSCLC

5. Patients must have experienced disease progression or recurrence after both a platinum-based chemotherapy regimen and at least 1 additional systemic therapy

   - Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate regimen of therapy

   - Prior platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease is considered first-line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy. Patients with recurrent disease >6 months must have received a subsequent platinum-based therapy regimen, which counts as their first –line of therapy.

6. Patient's tumour sample must be assessed as PD-L1-positive (where positive is defined as ≥25% of tumour cells with membrane staining [proprietary PD-L1 immunohistochemistry assay; Ventana Medical Systems, Inc]) (for Sub-study A) or PD-L1-negative (ie, those with <25% of tumour cells with membrane staining) (for Sub-study B) (either recent or archival sample) based on central assessment. Sample requirements as follows:

   - Patients must be able and willing to give valid written consent to provide newly acquired tumour tissue (preferred) or archival tissue (≤3 years old) for the purpose of establishing PD-L1 status (for collection and processing procedures, refer to Section 6.7.1 and the Laboratory Manual). Tumour lesions planned for biopsy must not be used as index lesions for assessment of disease, 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.

   - If the patient's PD-L1 status has already been assessed using the analytically validated Ventana assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.
     In addition to the samples used for determining PD-L1 status, patients are required to provide an archived tumour tissue block (or at least 10 newly cut unstained slides) where such samples exist in a quantity sufficient to allow for analysis (Refer to Section 6.7.1 and the Laboratory Manual for details).

7. Patients must have measurable disease, at least 1 lesion, not previously irradiated, which can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes that must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements per RECIST v1.1 guidelines

8. Life expectancy ≥12 weeks at Day 1

9. WHO Performance Status of 0 or 1

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

- Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution

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

11. Adequate organ and marrow function as defined below:

- Absolute neutrophil count >1.5 × 10^9/L (1500 per mm^3)

- Platelets >100 × 10^9/L (100,000 per mm^3)

- Haemoglobin ≥9.0 g/dL (5.59 mmol/L)

- Serum creatinine clearance (CL) >40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

  Males:

  - Creatinine CL (mL/min) = Weight (kg) × (140 – Age) / 72 x serum creatinine (mg/dL)

  Females:

  - Creatinine CL (mL/min) = Weight (kg) x (140 – Age) × 0.85 / 72 × serum creatinine (mg/dL)

- Serum bilirubin ≤1.5 x upper limit of normal (ULN). This will not apply to

patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinaemia that is predominantly unconjugated in the absence of evidence of haemolysis or hepatic pathology) who will be allowed in consultation with their physician.

- In patients with no liver metastasis: AST and ALT ≤2.5 × ULN
- In patients with liver metastasis: AST or ALT ≤5 × ULN.
- For patients receiving Standard of care, patients should fulfil the relevant requirements in the local prescribing information.

Genetics research study (optional)

CCI [redacted]

4.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca/MedImmune staff and/or staff at the study site)
2. Either:
   - Previous drug assignment in the present study
   - Prior treatment in a previous durvalumab (MEDI4736) clinical study
3. Participation in another clinical study with an investigational product during the last 4 weeks
4. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study
5. Mixed small cell and non-small cell lung cancer histology
6. Patients with known EGFR TK activating mutations or ALK rearrangements. Patients with EGFR TK inactivating mutations eg, exon 20, are eligible (Yasuda et al 2012). Note: Prospective testing is not planned within this study.

7. Receipt of any investigational drug within 4 weeks prior to the first dose of study drug.

8. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolisation, mAbs) ≤21 days prior to the first dose of study drug (≤14 days prior to the first dose of study drug for patients who have received prior TKIs [eg, erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C). If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca/MedImmune and the investigator.

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

10. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody

11. Any unresolved toxicity CTCAE >Grade 2 from previous anti-cancer therapy. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by study treatment may be included (eg, hearing loss) after consultation with the AstraZeneca/MedImmune medical monitor.

12. Any prior Grade ≥3 irAE while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1

13. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).

14. Receipt of radiation therapy within 4 weeks prior to starting study treatment. Limited field of radiation for palliation within 2 weeks of the first dose of study treatment is allowed:

    - Provided the lung is not in the radiation field
    - Provided irradiated lesion(s) cannot be used as target lesions.

15. Recent major surgery within 4 weeks prior to entry into the study (excluding the placement of vascular access) that would prevent administration of study treatment

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

17. Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)

18. History of primary immunodeficiency

19. History of allogeneic organ transplant

20. History of hypersensitivity to MEDI4736, or the active comparators (erlotinib gemcitabine or vinorelbine), or any excipient of these agents

21. Brain metastases or spinal cord compression unless asymptomatic, treated and stable off steroids and anti-convulsants for at least 1 month prior to entry into the study

22. History of leptomeningeal carcinomatosis

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

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

25. Active infection of tuberculosis, as determined by clinical signs and symptoms

26. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study treatment

27. History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ, and the disease under study, 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

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

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

30. Absence of a tumour sample (archival and recent).

Genetics research study (optional)

CCI [redacted]

Additional exclusion criteria for Sub-study B

31. Receipt of any prior mAb against CTLA-4.

32. History of chronic inflammatory or autoimmune disease (eg, Addison's disease,multiple sclerosis, Grave's disease, Hashimoto's thyroiditis, rheumatoid arthritis,hypophysitis, uveitis) with symptomatic disease within the last 3 years prior to enrolment. Note: Active vitiligo or alopecia or a history of vitiligo will not be a basis for exclusion.

33. Active or history of diverticulitis. Note: Diverticulosis is permitted.Active or history of inflammatory bowel disease (eg, colitis, Crohn's disease), irritable bowel disease, celiac disease, or other serious GI chronic conditionsassociated with diarrhoea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis.

34. History of sarcoidosis syndrome.

35. History of hypersensitivity to compounds of similar biologic composition to tremelimumab or any constituent of the product

4.3 Criteria for Treatment through Progression of Disease and Retreatment

Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible for continuing MEDI4736.

For all patients who completed the first 12 month period of treatment with MEDI4736 and had CR, PR or SD at completion, retreatment during follow-up would be offered on the basis of a patient having objective RECIST 1.1 disease progression with or without confirmation.

For all patients who are treated through progression, and patients who achieve disease control [ie, CR, PR, or SD] at 12 months and restart treatment upon evidence of PD during follow-up,the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing or restarting treatment would not further benefit the patient. In addition the investigator should ensure patients meet the following inclusion criteria (criteria number from Section 4.1):

- The patient must provide signed, written and dated retreatment or treatment through progression informed consent (criterion 1). This consent document for retreatment will specify that treatment beyond initial evidence of PD or retreatment upon progression during follow-up is not the standard of care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population.

- Meet serum creatinine CL >40 mL/min by the Cockcroft-Gault formula (or by 24-hour urine collection as defined by the formula in protocol inclusion criterion 11) and the criterion for AST/ALT.

The patient should not enter retreatment if any of the following exclusion criteria are fulfilled:

- Concurrent enrolment in another clinical study, unless it is an observational (non interventional) clinical study or the follow-up period of an interventional study (criterion 4)

- Current use of immunosuppressive medication, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid (criterion 9)

- Any unresolved toxicity CTCAE >Grade 2 from previous anti-cancer therapy. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (eg, hearing loss) after consultation with the AstraZeneca/MedImmune study physician (criterion 11)

- Any prior Grade ≥3 irAE while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1 (criterion 12)

- Be currently receiving, or have received in the interim period after stopping study drug, any chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Note: Local treatment of isolated lesions, excluding target lesions, for

palliative intent is acceptable (eg, by local surgery or radiotherapy) (drawn from criterion 13)

- Recent major surgery within 4 weeks prior to retreatment (excluding the placement of vascular access) that would prevent administration of investigational product (criterion 15)
- Active or prior documented autoimmune disease within the past 2 years (patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment within the past 2 years are not excluded) (criterion 16)
- Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis) (criterion 17)
- History of primary immunodeficiency (criterion 18)
- History of allogeneic organ transplant (criterion 19)
- History of hypersensitivity to MEDI4736 or any excipient (criterion 20)
- Brain metastases or spinal cord compression unless asymptomatic, treated and stable off steroids and anti-convulsants for approximately 1 month prior to first dose; timing will be at the discretion of the Principal Investigator (criterion 21)
- History of leptomeningeal carcinomatosis (criterion 22)
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction (criterion 23)
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any patient known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the patient to give written informed consent (criterion 24)
- Active infection of tuberculosis, as determined by clinical signs and symptoms (criterion 25)
- Receipt of live attenuated vaccination within 30 days prior to retreatment or within 30 days of receiving MEDI4736 (criterion 26)
- Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (criterion 28)

- Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of patient safety or study results (criterion 29)

- For sub-study B only: History of hypersensitivity to compounds of similar biologic composition to tremelimumab or any constituent of the product (criterion 35)

In the MEDI4736 and tremelimumab monotherapy arms, study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

At the time of final DCO, study patients who are receiving re-treatment will remain in the study. Patients who are in progression-free follow up at the time of the final DCO will be eligible for re-treatment at the time of progression if the investigator feels that re-treatment is the best treatment option and the patient meets the above eligibility criteria. Patients' eligibility should be recorded in their medical records.

5. STUDY CONDUCT

5.1 Restrictions during the study

1. **MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab:** Females of childbearing potential who are sexually active with a nonsterilised male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 90 days (MEDI4736 monotherapy) after the final dose of MEDI4736 or 180 days (MEDI4736+tremelimumab and tremelimumab monotherapy) after the final dose of tremelimumab; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

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

   – Patients must use 2 acceptable methods of effective contraception as described in Table 11.

2. **MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab:** Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 11) from Day 1 and for 90 days (MEDI4736) after the

final dose of MEDI4736 or 180 days (MEDI4736+tremelimumab and tremelimumab monotherapy) after the final dose of tremelimumab.

Table 11 Effective methods of contraception (2 methods must be used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	Combined pill
		Minipill
		Patch

[a] This is also considered a hormonal method.

3. **Standard of Care:** Follow the local prescribing information relating to contraception and the time limit for such precautions for agents in the Standard of Care arm (eg, gemcitabine prescribing information, NAVELBINE® prescribing information, TARCEVA® prescribing information).

4. **MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab:** Patients should not donate blood whilst participating in this study

5. **MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab:** During the study patients may receive palliative radiotherapy at the site of bone metastases that were present at baseline, providing the investigator does not feel that the bone pain is indicative of clinical disease progression. If a patient has further bone pain for which a second course of palliative radiation therapy is considered, the patient should be discussed with the QuintilesIMS Physician to decide if it is necessary for a patient to be discontinued from study treatment. The need for radiotherapy to any other site should be discussed with the QuintilesIMS Physician and any decisions will be made on a case-by-case basis.

6. **Standard of Care arm**: Please refer to the local prescribing information for the relevant product for any additional restrictions (eg, gemcitabine prescribing information, NAVELBINE® prescribing information, TARCEVA® prescribing information).

Restrictions relating to concomitant medications are described in Section 5.6.

5.2 Patient enrolment and randomisation

At Pre-screening, the Principal Investigator, or suitably trained delegate, will:

1. Obtain signed informed consent (Pre-screening Informed Consent Form) from the potential patient before any study specific procedures are performed.

2. Assign the potential patient a unique 7-digit enrolment number, beginning with 'E#'. This is obtained through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) (ECCNNXXX: CC being the country code, NN being the centre number, XXX being the patient enrolment code at the centre). Enrolment codes will start at 001 in each centre and go up sequentially (eg, at Centre 01, patients will be assigned E codes E0101001, E0101002, etc). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

3. Determine preliminary patient eligibility (investigator's opinion).

4. Send patient's tumour sample for pre-screening PD-L1 status.

Before Day 1, the Principal Investigator, or suitably trained delegate, will:

5. Obtain signed informed consent for the relevant sub-study, based on PD-L1 status (Sub-study A or Sub-study B Informed Consent Form) from the patient before any study treatment is given.

6. Assign patients to the respective sub-study based on PDL-1 status: PDL-1-positive NSCLC patients will be assigned to Sub-study A and PD-L1-negative NSCLC patients will be assigned to Sub-study B. This assignment step will take place within IVRS/IWRS.

7. Determine formal patient eligibility for each sub-study. See Sections 4.1 and 4.2.

8. Define the Standard of Care treatment (based on the most appropriate option for the patient) that the patient would receive if randomised to the Standard of Care arm prior to randomisation of the patient.

At Day 1 (randomisation [Baseline]), once the patient is confirmed to be eligible for either Sub-study A or B, the Principal Investigator, or suitably trained delegate, will:

9. Call IVRS/IWRS to assign the eligible patient a unique randomisation code (patient number). Randomisation codes will be assigned strictly sequentially by IVRS/IWRS, as patients are eligible for randomisation.

Patients may be enrolled but not randomised. If the patient is not randomised, the IVRS/IWRS should be contacted to terminate the patient in the system. The IVRS/IWRS will also be used to track drug supply.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused and they cannot re-enter into the study.

Histology will be determined for all patients prior to randomisation (ie, squamous or all other).

The sub-studies may not run concurrently with the start and completion of recruitment potentially occurring at different time points.

Procedures for randomisation

Patients must not be randomised unless all eligibility criteria have been met.

Standard of care treatment will be defined prior to randomisation and thus prior to treatment allocation. The Standard of Care treatment that the patient would be administered, should the patient be randomised to Standard of Care treatment arm, will be chosen by the investigator prior to randomisation. Patients will be randomised as follows.

NSCLC patients with PD-L1-positive tumours will be randomised in a 1:1 ratio to either:

(a) MEDI4736 (10 mg/kg Q2W iv) or

(b) Standard of Care (gemcitabine, vinorelbine or erlotinib)

in Sub-study A (approximately 60 patients in each arm).

NSCLC patients with PD-L1-negative tumours will be randomised in a 3:2:2:1 ratio (MEDI4736+tremelimumab:MEDI4736:Standard of Care:tremelimumab) to either:

(a) MEDI4736+tremelimumab (MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg Q4W iv up to 12 weeks [4 doses]) then MEDI4736 alone (10 mg/kg Q2W iv, starting at Week 16, for 34 weeks [18 doses]) (180 patients) or

(b) Standard of Care (gemcitabine, vinorelbine or erlotinib) (120 patients) or

(c) MEDI4736 (10 mg/kg Q2W iv) (120 patients) or

(d) Tremelimumab (10 mg/kg Q4W for 24 weeks then Q12W for 24 weeks iv) (60 patients)

in Sub-study B.

Patients will be stratified at randomisation based on the Standard of Care treatment that they would be administered (2 categories: gemcitabine/vinorelbine versus erlotinib) and histology (2 categories: squamous versus all other).

A separate randomisation list will be produced for each of the sub-studies within this protocol.

The actual treatment given to patients will be determined by the randomisation scheme in the IVRS/IWRS. The randomisation scheme for Sub-study A will be produced by a computer software programme called GRand (AstraZeneca Global Randomisation system) that incorporates a standard procedure for generating randomisation numbers. The randomisation scheme for Sub-study B will be produced by a computer software programme called RANGEN (Parexel randomisation generating system) that incorporates a standard procedure for generating randomisation numbers. A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment arm.

Patients will be identified to the Centralised Randomisation Centre per country regulations. Randomisation codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomisation. The IVRS/IWRS Centralised Randomisation Centre will inform the pharmacist of the kit identification number to be allocated to the patient at the randomisation visit.

Every effort should be made to minimise the time between randomisation and starting treatment. It is recommended that patients commence study treatment as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS system) and no later than 48 hours after randomisation.

Please note that all 'Week 0' study procedures per Table 3, Table 4, Table 5, Table 8 and Table 9 (dependent upon treatment arm) should be conducted on the same day and before (unless otherwise stated) the first administration of IP.

The investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new kit identification number. The kit identification number dispensed at each visit will correspond to the treatment to which the patient was originally randomised.

If a patient discontinues participation in the study, then their enrolment/randomisation code cannot be reused.

The IVRS/IWRS may not be available after the final DCO. In this case a manual process will need to be followed.

5.3 Procedures for handling patients incorrectly enrolled or randomised or initiated on study treatment

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study treatment. There can be no exceptions to this rule.

Where patients that do not meet the inclusion and/or exclusion criteria, are enrolled in error, are randomised in error, or are incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion must occur between the QuintilesIMS Physician and the investigator regarding the patient's safety and well-being and whether to continue or discontinue the patient from study treatment.

The QuintilesIMS Physician is to ensure all such contacts are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study treatment stopped, then be followed up where possible as per Section 5.8.1. Those patients randomised in error should remain in the study and be followed for OS and PFS where possible.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study centre pharmacist will be unblinded to study treatment and will prepare MEDI4736 and tremelimumab or the relevant Standard of Care for a patient as specified by the randomisation scheme and IVRS (the investigator will call into IVRS to obtain the randomisation/treatment allocation details). Pharmacists will be given specific instructions for study drug preparation. Lot numbers of study drug dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. The patient, the investigator and study centre site staff will also be unblinded to study drug allocation.

However, no member of the extended study team at AstraZeneca/MedImmune will have access to the randomisation scheme nor will conduct any aggregate analysis by treatment arm until the time of the final data analysis. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca/MedImmune or their designee, where the information is needed to package study treatment and the drug safety departments at AstraZeneca/MedImmune.

Where possible, site staff should avoid giving information to parties outside the site team in case it leads to unblinding.

5.4.2 Methods for unblinding the study

This will be applicable for the AstraZeneca global team only. In order to provide proper oversight of the toxicity management AstraZeneca/MedImmune retains the right for the patient safety representative and the study physician to be provided with SAE reports which are unblinded. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

AstraZeneca will supply MEDI4736 and tremelimumab (Table 12).

Table 12 List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
MEDI4736	500 mg/vial solution after dilution	MedImmune
Tremelimumab	400 mg/vial solution for infusion after dilution	MedImmune

5.5.1.1 MEDI4736

The Pharmaceutical Development Supply chain of AstraZeneca/MedImmune will supply MEDI4736 to the investigator as a 500-mg vial solution for infusion after dilution in 1 format for use throughout the study or sub-study.

The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) 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 either 10 mg/kg or 20 mg/kg will be administered using an iv bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final MEDI4736 concentration in the bag ranging from 1 to 20 mg/mL, delivered through an iv administration set with a 0.2- 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% (weight/volume) saline or 5% (weight/volume) 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, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

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

All details can be found in the Drug Handling Instructions.

Dose calculation of MEDI4736

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

Both sub-studies (monotherapy and combination arms)

$$10 \text{ mg/kg} \times \text{Patient Weight (kg)} \div \text{MEDI4736 concentration (nominal: 50 mg/mL)}$$

Sub-study B (combination arm)

20 mg/kg × Patient Weight (kg) ÷ MEDI4736 concentration (nominal 50 mg/mL)

Example: For a patient weighing 80 kg, dosed at 20 mg/kg, 32 mL [20 mg/kg × 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in a 250 mL iv bag containing 0.9% (weight/volume) saline or 5% (weight/volume) dextrose. First, 32 mL of iv diluent (saline or dextrose) 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.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Table 13 summarises time allowances and temperatures.

Table 13 MEDI4736 in-use stability and infusion times

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

iv Intravenous.

In the event that either preparation time or infusion time exceeds the time limits outlined in Table 13, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded. All details can be found in the Drug Handling Instructions.

5.5.1.2 Tremelimumab

The Pharmaceutical Development Supply chain of AstraZeneca/MedImmune will supply tremelimumab to the investigator.

Tremelimumab is supplied as a sterile iv solution, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, 0.27 mM disodium edetate dihydrate (EDTA), at pH 5.5. The standard supply of tremelimumab is delivered in a white carton with 16 vials of tremelimumab within foam inserts. Tremelimumab vials should be stored at refrigerated temperatures (2°C to 8°C), and should not be frozen.

Preparation of tremelimumab doses for administration with an iv bag

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

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

Doses of 1 mg/kg and 10 mg/kg tremelimumab will be administered using an iv bag containing 0.9% (w/v) saline, with a final tremelimumab concentration in the iv bag 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 ≥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% (weight/volume) saline equal to the calculated volume of tremelimumab to be added to the iv bag must be removed from the bag prior to addition of tremelimumab. The calculated volume of tremelimumab is then added to the iv bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Intravenous bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (eg, polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP free. Catheters/infusion sets made of polyurethane or fluoropolymer with silicone and stainless steel and/or PVC components can be used for tremelimumab administration. Syringes should be made of polypropylene and latex-free. Polycarbonate syringes should not be used with tremelimumab. Stainless steel needles need to be used.

All details can be found in the Drug Handling Instructions.

Dose calculation of tremelimumab

The volume of tremelimumab (in mL) to be added to the iv bag will be calculated using the following formula:

Either:

Sub-study B (combination arm)

1 mg/kg × Patient Weight (kg) ÷ tremelimumab concentration (nominal 20 mg/mL)

Sub-study B (monotherapy arm)

10 mg/kg × Patient Weight (kg) ÷ tremelimumab concentration (nominal 20 mg/mL)

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

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Table 14 summarizes time allowances and temperatures.

Table 14 Tremelimumab in-use stability and infusion times

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

iv Intravenous.

In the event that either preparation time or infusion time exceeds the time limits outlined in Table 14, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded. All details can be found in the Drug Handling Instructions.

5.5.1.3 Standard of Care

The comparator arm of this study is Standard of Care; this is restricted to gemcitabine, vinorelbine or erlotinib (Table 15). These will be sourced centrally.

Table 15 Standard of Care

Standard of Care	Dosage form and strength	Manufacturer
Gemcitabine	1000 mg vials 1000 mg/m^2 intravenously over 30-minutes on Days 1, 8, and 15 of a 28-day cycle	Eli Lilly and Company or relevant manufacturer if a generic equivalent is used
Vinorelbine	50 mg vials 30 mg/m^2 intravenously on Days 1, 8, 15 and 22 of a 28 day cycle	Pierre Fabre Pharmaceuticals, Inc. for GlaxoSmithKline or relevant manufacturer if a generic equivalent is used

Erlotinib	25 mg and 100 mg as required for dosing 150 mg once daily as tablets for oral administration taken at least 1 hour before or 2 hours after the ingestion of food	Genentech, Roche, or Chugai Pharmaceuticals

5.5.2 Doses and treatment regimens

It is important to follow the assessment schedule as closely as possible.

Treatment delays

All visits should be conducted based on the schedules provided in Table 3 to Table 10, unless otherwise indicated.

For all treatment arms

- Tumour efficacy (RECIST 1.1) assessments dates are not affected by dose delays, and remain as originally scheduled, because they are based on the date of randomisation (not the date of therapy).
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures required for dosing should be performed within 3 days prior to dosing.

For MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab combination arms

Patients may delay dosing under certain circumstances:

- Dosing may be delayed due to either an immune or a non-irAE as per Toxicity Management Guidelines (Refer to Section 5.5.3).
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
- Dosing intervals of subsequent cycles in the combination arm may be shortened as clinically feasible and in line with the treatment windows in order to gradually align treatment cycles with the schedule of tumour efficacy (RECIST 1.1) assessments.

5.5.2.1 MEDI4736 monotherapy (Sub-study A and Sub-study B)

Patients randomised to MEDI4736 monotherapy in either sub-study will receive 10 mg/kg via iv infusion Q2W ±3 days. Treatment with MEDI4736 will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a Q2W schedule for up to 12 months (see Table 3). The final administration of MEDI4736 will be at the Week 50 visit.

Study treatment should be discontinued prior to 12 months if there is PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Disease progression that occurs while on treatment requires confirmation. In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study treatment until progression has been confirmed. If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

Patients in the MEDI4736 monotherapy arms who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month MEDI4736 treatment period will enter follow-up (Table 6). Upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up after completion of 12 months of treatment, patients may restart treatment with MEDI4736 for as long as the investigator judges they are gaining clinical benefit with the same treatment guidelines followed during the initial 12-month treatment period (Table 3). Patients will only be able to restart treatment once.

Patients who have a dose interruption due to toxicity at any point in the first 12 months of treatment may resume and complete the 12-month treatment period.

Patients who have confirmed PD during the 12-month initial treatment period, or after restarting MEDI4736 and cannot continue to receive MEDI4736 will enter follow-up with assessments as shown in Table 7. Patients with confirmed PD that continue to receive MEDI4736 at the discretion of the investigator (following consultation with the sponsor) can receive study drug for a maximum of 12 months in the initial treatment period but for as long as the investigator judges they are gaining clinical benefit in the re-treatment period (and will follow the assessments in Table 3 including tumour assessments).

Administration

Following preparation of MEDI4736, the entire contents of the iv bag should be administered as an iv infusion over approximately 60 minutes (±5 minutes), using a 0.2- or 0.22-µm in-line filter. The iv line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the iv bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed. Since the compatibility of MEDI4736 with other iv medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection), or 5% dextrose is not known, the MEDI4736 solution should not be infused through an iv line in which other solutions or medications are being administered. The date, start time, interruption and completion time of MEDI4736 administration must be recorded in the source documents.

5.5.2.2 MEDI4736+tremelimumab and tremelimumab monotherapy (Sub-study B)

MEDI4736+tremelimumab

Patients randomised to MEDI4736+tremelimumab will receive MEDI4736 20 mg/kg and tremelimumab 1 mg/kg via iv infusion Q4W ±3 days for up to 12 weeks (4 doses) and then MEDI4736 10 mg/kg alone via iv infusion Q2W for 34 weeks starting at Week 16 (18 doses). Treatment with MEDI4736+tremelimumab will commence on Day 1 following randomisation after confirmation of eligibility (see Table 5). The final administration of the MEDI4736+tremelimumab combination will be at the Week 12 visit and the final administration of the MEDI4736 10 mg/kg monotherapy portion in the combination arm will be at the Week 50 visit.

In the combination arm, patients who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 4th cycle (Week 16, 4 weeks after the last dose of combination treatment) will continue with the planned treatment for this arm, ie, MEDI4736 10 mg/kg Q2W. If patients should experience PD (according to RECIST 1.1), with or without confirmation, during the MEDI4736 monotherapy treatment, retreatment with the combination regimen may begin.

Patients who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 12-month study drug treatment period will enter follow-up (Table 6). Patients may restart MEDI4736+tremelimumab upon evidence of PD (according to RECIST 1.1) with or without confirmation, during follow-up.

Any patient who is restarting the combination treatment regimen will adhere to the same treatment guidelines followed during the initial treatment period. Patients would resume MEDI4736 20 mg/kg Q4W as during the initial induction period, along with tremelimumab 1 mg/kg Q4W for 4 doses. Monotherapy with MEDI4736 10 mg/kg Q2W would then resume at Week 16, 4 weeks after the last dose of combination treatment, and treatment will continue for as long as the investigator judges they are gaining clinical benefit.

Patients will only be able to restart treatment once. Note that restarting of combination treatment can occur any time after Week 16.

Treatment should be discontinued prior to 50 weeks if there is confirmed PD during the initial combination regimen (ie, during the first 4 cycles) or if patients have confirmed PD after restarting MEDI4736+tremelimumab and cannot continue to receive MEDI4736+tremelimumab (or MEDI4736 monotherapy if on or after Week 16); these patients will enter follow-up with assessments as shown in Table 7. If initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reason to discontinue treatment occurs, these patients will enter follow-up with assessments as shown in Table 6. Patients with confirmed PD that continue to receive MEDI4736+tremelimumab at the discretion of the investigator (following consultation with the sponsor) can receive study drug for a maximum of 12 months in the initial treatment period but for as long as the investigator

judges they are gaining clinical benefit in the re-treatment period (and will follow the assessments in Table 5 including tumour assessments).

Patients who have a dose interruption due to toxicity at any point in the first 12 months of treatment may resume and complete the 12-months treatment period.

Tremelimumab monotherapy

Patients randomised to tremelimumab monotherapy will receive tremelimumab 10 mg/kg via iv infusion Q4W ±3 days up to Week 24 and then every 12 weeks up to a further 24 weeks. Treatment with tremelimumab will commence on Day 1 following randomisation after confirmation of eligibility (see Table 4) and continue until the Week 48 visit.

Study treatment should be discontinued prior to 48 weeks if there is PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Study treatment should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Disease progression that occurs while on treatment requires confirmation. In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study treatment until progression has been confirmed. If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

Patients in the tremelimumab monotherapy arm who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 48-week treatment period will enter follow-up (Table 6). Upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up after completion of 48 weeks of treatment, patients may restart treatment with tremelimumab monotherapy for as long as the investigator judges they are gaining clinical benefit with the same treatment guidelines followed during the initial 48-week treatment period (Table 4). Patients will only be able to restart treatment once.

Patients who have a dose interruption due to toxicity at any point in the first 48 weeks of treatment may resume and complete the 48 weeks treatment period.

Patients who have confirmed PD during the 48-week initial treatment period, or after restarting tremelimumab monotherapy and cannot continue to receive tremelimumab, will enter follow-up with assessments as shown in Table 7. Patients with confirmed PD that continue to receive tremelimumab at the discretion of the investigator (following consultation with the sponsor) can receive study drug for a maximum of 12 months in the initial treatment period but for as long as the investigator judges they are gaining clinical benefit in the re-treatment period (and will follow the assessments in Table 4 including tumour assessments).

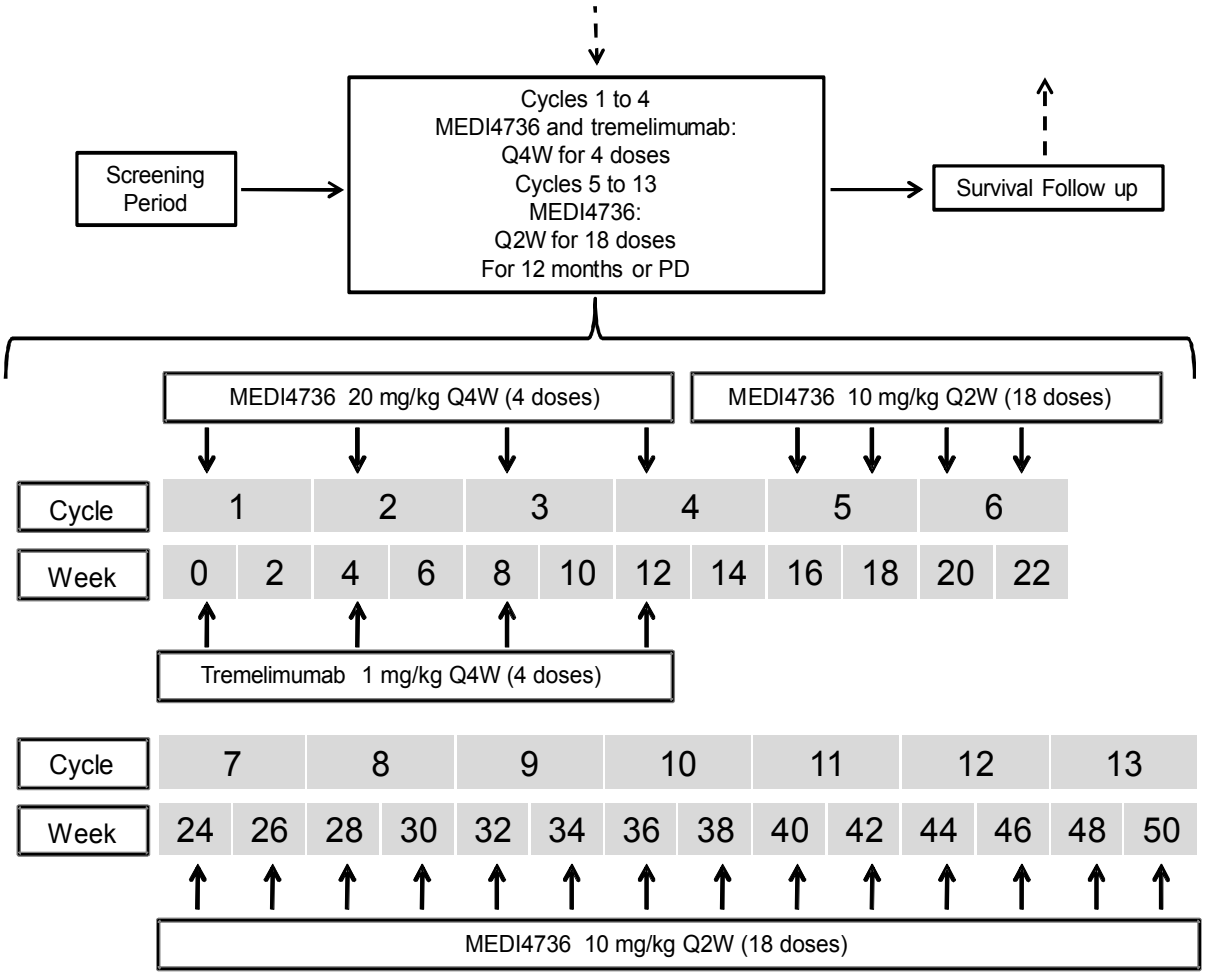
Administration of tremelimumab monotherapy

Following preparation of tremelimumab, the entire contents of the iv bag should be administered as an iv infusion over approximately 1 hour. The date, start time, interruption and completion time of tremelimumab administration must be recorded in the source documents.

Administration of MEDI4736+tremelimumab

Tremelimumab will be administered first. MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion for the first infusion only. If there are no clinically significant concerns after the first cycle, and at the discretion of the physician, in all other cycles the MEDI4736 can be given immediately after the tremelimumab infusion has finished. The duration of each infusion will be approximately 60 minutes (±5 minutes). After 4 doses, patients will receive MEDI4736 monotherapy (see Administration in Section 5.5.2.1).

Figure 5 Schema for MEDI4736+tremelimumab treatment



5.5.2.3 Monitoring of dose administration of MEDI4736 and/or tremelimumab

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in Section 6.4.8.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of MEDI4736 and tremelimumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. If, following 4 hours of interruption, there is persistent Grade 2 toxicity despite the use of appropriate medications such as antihistamines or acetaminophen, then study treatment should be discontinued. If, following 4 hours of interruption, there is a decrease to Grade 1, then the drug may be re-introduced if it does not present an increased risk to the patient. If the infusion-related reaction is ≥Grade 3 or higher in severity, treatment with MEDI4736 and/or tremelimumab 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 recognise and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

5.5.2.4 Dose and schedule of agents in the Standard of Care arm

The choice of Standard of Care used at study sites will be determined by the investigator at the local study sites. The Standard of Care treatment will be selected from the following restricted list: an EGFR TKI (ie, erlotinib) gemcitabine or vinorelbine. The investigator at the local study site will be responsible for the choice of the Standard of Care arm for an individual patient.

Treatment in the Standard of Care arm will commence on Day 1 following randomisation after confirmation of eligibility and will continue on a 4-weekly schedule until PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur.

Treatment through PD in the Standard of Care arm is at the investigator's discretion. In cases of unequivocal progression the investigator should discontinue treatment, where it is uncertain if disease has progressed the investigator should decide whether (if in the absence of clinically significant deterioration) to continue the patient on treatment until progression has been confirmed.

Gemcitabine

Gemcitabine should be administered at a dose of 1000 mg/m^2 iv over 30 minutes on Days 1, 8, and 15 (±3 days) of a 28-day cycle.

Section 5.5.3.3 details the recommended dose reductions for gemcitabine for myelosuppression in NSCLC.

Vinorelbine

Vinorelbine should be administered at a dose of 30 mg/m^2 iv on Days 1, 8, 15 and 22 (±3 days) of a 28-day cycle.

Vinorelbine should be administered either by slow bolus over 6 to 10 minutes after dilution in 50 mL of a 0.9% sodium chloride solution or by a short infusion over 20 to 30 minutes, after dilution in 125 mL of normal saline solution. Administration should always be followed by at least 250 mL normal saline infusion to flush the vein.

Section 5.5.3.3 details the dose modifications required based on the neutrophil count on the day of administration.

Erlotinib

Erlotinib should be administered at a dose of 150 mg once daily as a tablet for oral administration taken at least 1 hour before or 2 hours after the ingestion of food. Please refer to the local prescribing information particularly if the patient will receive concomitant cytochrome P450 (CYP) 3A4 inducers or is a smoker (as increases in the dose may be required) or is receiving concomitant treatment with a drug that may affect gastric pH.

For all Standard of Care agents, please refer to Section 5.5.3.3 for details of recommended dose modifications in the event of toxicities.

5.5.2.5 Treatment through progression of disease

Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period will enter follow-up. When these patients experience evidence of PD, with or without confirmation, during follow-up and meet the criteria for treatment in the setting of PD, they will be given the option to restart their assigned immune-mediated cancer treatment (ie, MEDI4736 monotherapy, tremelimumab monotherapy or combination MEDI4736+tremelimumab) for as long as the investigator judges they are gaining clinical benefit with the same treatment guidelines followed during the initial 12-month treatment period. Patients should have a baseline tumour assessment within 28 days before restarting their assigned immune-mediated cancer treatment; all further scans should occur every 8 weeks (relative to the date of restarting treatment) until study treatment is stopped. Only patients who the investigator determines do not have any significant, unacceptable, or irreversible toxicities, or would continue to receive benefit from therapy can restart a second 12 months of retreatment upon PD.

Patients with confirmed progression in the MEDI4736 monotherapy or tremelimumab monotherapy arms cannot continue treatment or obtain retreatment if the progression occurred during treatment and after confirmed response (ie, the response and progression events both occurred while receiving active immune-mediated cancer treatment during the same treatment period).

Retreatment in the MEDI4736+tremelimumab arm can only occur if PD, with or without confirmation, occurs during the monotherapy portion or after completion of 12 months of treatment. During the retreatment period, the patient would resume MEDI4736 20 mg/kg Q4W as during the initial induction period, along with tremelimumab 1 mg/kg Q4W for 4 doses. Monotherapy with MEDI4736 10 mg/kg Q2W would then resume at Week 16, 4 weeks after the last dose of combination treatment, and can continue for as long as the investigator judges they are gaining clinical benefit.

For patients who receive study treatment through disease progression and patients who achieve disease control (ie, CR, PR or SD) and restart treatment, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient**.** The patient must meet the inclusion and exclusion criteria specified in Section 4.3. The informed consent documents will specify that treatment beyond initial evidence of PD or re-treatment for progression during follow-up is not the standard of care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive treatment.

5.5.3 Management of toxicity

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

1. Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).

2. If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of study treatments along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (see below).

3. All dose modifications should be documented with clear reasoning and documentation of the approach taken.

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy are provided in the Dosing Modification and Toxicity Management Guidelines (TMGs). Please see Appendix H.

The most current version of the TMGs is also available through the following link: https://tmg.azirae.com. In addition a version of the current TMGs is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

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

In addition, there are certain circumstances in which study treatment should be permanently discontinued (see Section 5.8 of this protocol and the TMGs).

These guidelines have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

5.5.3.1 Management of toxicity attributable to MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab

The guidance that should be followed for management of toxicities is presented in the Dose Modification and Toxicity Management Plan in Section 5.5.3.

Following the first infusion of MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab (ie, the study drug), subsequent administration of the study drug can be modified based on toxicities observed as described in the TMGs. These guidelines have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

All toxicities will be graded according to CTCAE Version 4.03. Dose reductions are not permitted.

Dose modifications will not be required for AEs that are clearly not attributed to the study drug (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo of any AE grade.

Based on the mechanism of action of MEDI4736 and tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and nivolumab including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Brahmer et al 2010, Hodi et al 2010). Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate aetiology (eg, infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

5.5.3.2 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.

More specific guidelines for the evaluation and treatment of these adverse events of special interest are described in detail in Section 5.5.3. These guidelines have been prepared by the Sponsor to assist the investigator in exercising his/her judgement in treating these toxicities.

MEDI4736 adverse events of special interest

The AESIs for MEDI4736 include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy. An irAE is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the investigator has any questions in regards to an AE being an irAE, the investigator should promptly contact the Study Physician.

AESIs observed with MEDI4736 with or without tremelimumab include, but are not limited to:

- Diarrhea/colitis and intestinal perforation
- Pneumonitis/interstitial lung disease
- Hepatitis/transaminase increases
- Endocrinopathy (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 (eg, 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 the TMGs (Refer to Section 5.5.3).

Tremelimumab adverse events of special interest

Detailed information on the risks (eg, presenting symptoms) associated with tremelimumab can be found in the current version of the tremelimumab IB.

5.5.3.3 Management of toxicity attributable to agents in the Standard of Care arm

Information on recommended dose reductions are provided for each Standard of Care agent below; however, please refer to the relevant local prescribing information for the relevant agent.

Gemcitabine

Recommended dose reductions for gemcitabine for myelosuppression in NSCLC are provided in Table 16.

Table 16 Dose reduction for gemcitabine for myelosuppression in NSCLC

Absolute granulocyte count ($x10^6$/L)		Platelet count ($x 10^6$/L)	% of full dose
≥1000	AND	≥100,000	100
500-999	OR	50,000-99,999	75
<500	OR	<50,000	Do not administer

Gemcitabine should be permanently discontinued for any of the following non-haematologic adverse reactions: unexplained dyspnoea or other evidence of severe pulmonary toxicity; severe hepatic toxicity; haemolytic-uremic syndrome, or capillary leak syndrome.

Gemcitabine should be withheld or the dose reduced by 50% for other severe (Grade 3 or 4) non-haematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

Vinorelbine

Adjustments in the dosage of vinorelbine should be based on neutrophil counts obtained on the day of treatment (Table 17).

Table 17 Vinorelbine dosing based on neutrophil counts

Neutrophils (cells/mm^3) on day of treatment	Dose of vinorelbine (mg/m^2)
≥1500	30
1000-1499	15
<1000	Do not administer. Repeat neutrophil count in 1 week. If 3 consecutive weekly doses are held because neutrophil count is <1000 cells/mm^3, vinorelbine should be discontinued.

For patients who, during treatment with vinorelbine, experience fever and/or sepsis while neutropenic or have 2 consecutive weekly doses withheld due to neutropenia, the subsequent doses of vinorelbine should be: 22.5 mg/m^2 for neutrophil counts ≥1500 cells/mm^3 or 11.25 mg/m^2 for neutrophil counts between 1000 to 1499 cells/mm^3.

For European sites only:

In accordance with approved prescribing information for Navelbine 10 mg/mL concentrate for solution for infusion, if the neutrophil count is below 1500/mm^3 and/or the platelet count is below 100000/mm^3, then the treatment should be delayed until recovery.

The dose of vinorelbine should be adjusted for total bilirubin for patients who develop hyperbilirubinaemia during treatment (Table 18).

Table 18 Vinorelbine dosing based on total bilirubin

Total bilirubin (mg/dL)	Dose of vinorelbine (mg/m^2)
≤2.0	30
2.1-3.0	15
>3.0	7.5

In patients with both haematologic toxicity and hepatic insufficiency, the lower of the doses based on the corresponding starting dose of vinorelbine should be used, as determined from Table 17 and Table 18.

If ≤Grade 2 neurotoxicity develops, vinorelbine should be discontinued.

Erlotinib

The following dose modification rules for erlotinib should be applied:

- Follow local prescribing guidelines in cases of severe reactions with concomitant use of strong CYP3A4 inhibitors or when using concomitantly with an inhibitor of both CYP3A4 and CYP1A2 (eg, ciprofloxacin). Dose reductions may be required. Avoid concomitant use if possible.

- Follow local prescribing guidelines when restarting therapy following withholding treatment for a DLT that has resolved to baseline or Grade ≤1. Dose reductions may be required.

Erlotinib should be withheld in the following circumstances:

- During diagnostic evaluation for possible interstitial lung disease

- For severe (CTCAE Grade 3/4) renal toxicity; consider discontinuation of erlotinib

- In patients without pre-existing hepatic impairment for total bilirubin levels >3 × ULN or transaminases >5 × ULN; consider discontinuation of erlotinib

- In patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline; consider discontinuation of erlotinib

- For persistent severe diarrhoea not responsive to medical management (eg, loperamide)

- For severe rash not responsive to medical management

- For CTC (Version 4.0) Grade 3/4 keratitis or for Grade 2 keratitis lasting more than 2 weeks

- For acute/worsening of ocular disorders such as eye pain; consider discontinuation of erlotinib.

Erlotinib should be discontinued in the event of: interstitial lung disease, severe hepatic toxicity that does not improve significantly or resolve within 3 weeks, gastrointestinal perforation, severe bullous, blistering, or exfoliating skin conditions, or corneal perforation or severe ulceration.

5.5.4 Additional study drug

No additional study drug is required in this study.

5.5.5 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- Name of sponsor (AstraZeneca)
- Study treatment dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study code
- Enrolment code
- Directions for use
- The period of use eg, expiry date.
- Product Lot Identifier
- Medication Identity Number
- For clinical study use only
- Keep out of reach of children (if the study treatment is to be taken home by the patient).

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

5.5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. The product label on the kit specifies the appropriate storage.

Standard of Care agents should be stored per the manufacturer's recommendations.

5.6 Concomitant and post-study treatment(s)

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed below:

- Any investigational anti-cancer therapy
- Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).
- For patients in the immune therapy arms, immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor alpha blockers should not be given concomitantly. Use of immunosuppressive medications in patients for the management of study treatment-related AEs or their use in patients with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. 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).
- Live attenuated vaccines within 30 days of dosing. Inactivated viruses such as those in the influenza vaccine are permitted.
- For agents used in the Standard of Care arm, please also refer to the local prescribing information with regards to warnings, precautions and contraindications.
- For patients receiving tremelimumab monotherapy (10 mg/kg), drugs with laxative properties and herbal or natural remedies for constipation should be avoided for 90 days after the last dose of study drug.
- For patients on the MEDI4736+tremelimumab combination arm, drugs with laxative properties and herbal or natural remedies for constipation should be used with caution for 90 days after the last dose of tremelimumab.
- For patients in the tremelimumab monotherapy and MEDI4736+tremelimumab combination arms, sunitinib should not be given concomitantly or for 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib).

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

5.7 Treatment compliance

Treatment compliance will be assured by site reconciliation of study treatment dispensed.

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. The investigator or pharmacy must retain records of all study drugs administered. The study monitor will check these records to confirm the compliance with the protocol administration schedule. Administration of study drug as re-treatment following final DCO will be recorded in site documents for the purpose of supply management but will not otherwise be reported.

Any dose reductions will be documented, along with reasons for the dose reduction.
Note: No dose reductions are allowed for MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 13.2 for procedures in case of overdose.

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 dispensed to and returned from the patient.

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

5.8 Discontinuation of study treatment

Patients may be discontinued from study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event, that in the opinion of the investigator or the sponsor, contraindicates further dosing
- Severe non-compliance to study protocol that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits

- Patient is determined to have met 1 or more of the exclusion criteria for study participation at study entry and continuing study treatment might constitute a safety risk

- Any AE that meets criteria for discontinuation, as defined in Section 5.5.3 for MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab or as defined in the local prescribing information for agents in the Standard of Care arm

- An AE related to study treatment that is ≥Grade 3, with the exception of toxicities that do not meet criteria for discontinuation as defined in Section 5.5.3 for MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab or as defined in the local prescribing information for agents in the Standard of Care arm

- ≥Grade 3 infusion reaction (does not apply to patients receiving erlotinib)

- Initiation of alternative anti-cancer therapy including another investigational agent

- Confirmed PD and investigator determination that the patient is no longer benefiting from treatment. Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

- Pregnancy or intent to become pregnant.

If the patient is discontinued from study treatment, the scheduled study visits, data collection and procedures should continue according to this study protocol until study closure. Alternatively, if the patient does not agree to this option, a modified follow-up through eg, regular telephone contacts or a contact at study closure should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices. See Section 5.8.1.

Following final DCO, only SAEs occurring up to 90 days after the last dose of MEDI4736 or tremelimumab will be reported directly to AstraZeneca Global Patient Safety as described in Section 6.4.4. Other AEs should be managed according to the toxicity management guidelines in Section 5.5.3, and will be followed up per the investigators' judgment but will not be otherwise reported or recorded for the purposes of this study. Following the final DCO, investigators who intend to commence or continue re-treatment with study drug should continue to monitor patients' safety laboratory assessments so as to ensure that no laboratory abnormalities or AEs that could potentially result in IP discontinuation are overlooked. All data will be recorded into the patients' charts but will not be otherwise documented for the purposes of this study.

Withdrawal of consent for PGx and biological sampling is included in Section 7.5.

5.8.1 Procedures for discontinuation of a patient from study treatment

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

A patient that decides to discontinue study treatment will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (see Sections 6.4.3 and 6.4.4), and questionnaires and all study drugs should be returned by the patient.

If a patient is withdrawn from the study, see Section 5.9.

5.8.2 Assessments following withdrawal of study treatment

Patients who are permanently discontinued from receiving study treatment will remain in the study and will be followed per the study plans for safety including the collection of any protocol-specified blood specimens and completion of questionnaires and eCRFs relating to PRO and hospital resource use, unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study. All patients will be followed for survival up to the time of final DCO. Patients who decline to return to the site for evaluations will be offered follow-up by phone as specified in the study plans as an alternative (MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10 [follow-up for patients treated with Standard of Care]). However, patients who discontinue due to an AE will need to attend all protocol-specified visits, and all assessments will be conducted as scheduled.

All patients who have any Grade 3 or 4 laboratory values at the time of discontinuation must have further tests performed and the results recorded on the appropriate eCRF until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

At discontinuation, all ongoing study-related toxicities and SAEs must be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

All new AEs occurring for up to 90 days after the last dose of study treatment (30 days after last dose of Standard of Care) must be recorded in the eCRF and reported as SAEs, if applicable.

Patients in the MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms who have disease control following completion of treatment or patients who are withdrawn from study treatment for reasons other than confirmed PD will continue to have objective tumour assessments (see MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: Table 6 [for follow-up of patients achieving

disease control or who are discontinued due to toxicity or a reason other than confirmed PD]). Drug or study procedure-related SAEs must be captured until the patient completes the follow-up period following discontinuation of study treatment (due to confirmed PD) or is permanently withdrawn from the study (see Section 5.9).

When confirmed PD has been documented, the long-term follow-up information for survival should be collected per the study plans (MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10) by telephone contact with the patient, patient's family, or by contact with the patient's current physician. An exception is any patient in the MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms with confirmed PD during the initial treatment period that continues to receive study treatment at the discretion of the investigator (MEDI4736, tremelimumab monotherapy or MEDI4736+tremelimumab patients can receive treatment for a maximum of 12 months/48 weeks as applicable). Retreatment may continue as long as the investigator judges the patient to be gaining clinical benefit. Patients will follow the assessments in the study plan [MEDI4736 monotherapy: Table 3, tremelimumab monotherapy: Table 4 or MEDI4736+tremelimumab: Table 5] including tumour assessments until study treatment is discontinued the patient must re-consent to be treated through disease progression [see Section 8.4]).

Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

Both the patient and the physician will be asked about the subsequent treatment the patient receives during the follow-up period per the study plans (MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity in or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10 [follow-up for patients treated with Standard of Care]).

5.9 Withdrawal from study

Patients may be discontinued from the study in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Severe non-compliance to study protocol that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits
- Patient lost to follow-up.

Patients are at any time free to withdraw from study (study treatment and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Section 6.4.3 and Section 6.4.4); and questionnaires and all study drugs should be returned by the patient.

If consent is withdrawn, the patient will not receive any further study treatment or further study observation. The patient will be specifically asked if they are withdrawing consent to:

- Further participation in the study including any further follow-up (eg, survival calls)
- Withdrawal of consent to the use of their study generated data
- Withdrawal to the use of any samples (see Section 7.5).

Note that the patient may be offered additional tests or tapering of treatment to withdrawal for safety, and will be offered follow-up by phone as specified in the study plans as an alternative (MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10 [follow-up for patients treated with Standard of Care]). If a patient wishes to withdraw their consent to further participation in the study, including survival follow-up (by phone) this should be clearly documented in the patient notes and in the clinical study database.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the patient's status at that time.

Note: Patients who refuse to continue participation in the study, including phone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient

should not be considered lost to follow-up and any evaluations should resume according to the protocol.

Withdrawn patients will not be replaced.

Vital status (ie, whether a patient is dead or alive), based on public available sources, will be investigated at the scheduled study end.

6. COLLECTION OF STUDY VARIABLES

MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: The schedule of study procedures at Screening and during the Treatment Period for MEDI4736 monotherapy is presented in Table 3, for tremelimumab monotherapy in Table 4 and for MEDI4736+tremelimumab in Table 5. The schedule of follow-up procedures for patients who have completed MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab and achieved disease control and patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab due to toxicity or a reason other than confirmed PD is presented in Table 6. The schedule of follow-up procedures for patients who have discontinued MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab due to confirmed PD is presented in Table 7. Following final DCO, no further study data will be captured except for SAEs (in the AstraZeneca Global Patient Safety database) for patients whilst the patient is either still receiving study drug, (ie, re-treatment patients) or is in the 90-day safety follow-up period after receiving the last dose of study drug. Investigators with patients in progression-free follow-up who may become eligible for re-treatment are to conduct scans/RECIST per local practice and safety laboratory assessments in such a way that alignment with per-protocol re-treatment eligibility criteria can be properly determined.

Standard of Care: The schedule of assessments for patients treated with vinorelbine or gemcitabine is presented in Table 8 and for patients treated with erlotinib is presented in Table 9. The schedule of follow-up procedures for patients treated with Standard of Care is presented in Table 10.

6.1 Recording of data

The InForm Web Based Data Capture (WBDC) system will be used for data collection and query handling until the point of final DCO and database lock for the study. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided. Data from the paper questionnaires will be transcribed at the investigator site onto the eCRF.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

The following assessments and procedures should be performed within the 42 days prior to the first dose of MEDI4736 (Table 3), tremelimumab monotherapy (Table 4), MEDI4736+tremelimumab (Table 5) or Standard of Care (Table 8 for patients who will receive gemcitabine or vinorelbine and Table 9 for patients who will receive erlotinib). For details of the nature of the assessments, see below:

- Signed informed consent for the Pre-screening Period of the study and assignment of a patient identification number
- Preliminary eligibility criteria (investigator's opinion)
- Demographic details including age, sex and ethnicity and also tobacco and alcohol consumption history
- Details on previous treatments for NSCLC
- A mandatory provision of a newly acquired tumour tissue (preferred) or archival (≤3 years) tumour biopsy (for collection and processing procedures, refer to Section 6.7.1 and the Laboratory Manual). In addition to the samples used for determining PD-L1 status, provision of an archived tumour tissue block (or at least 10 newly cut unstained slides) where such samples exist in a quantity sufficient to allow for analysis (Refer to Section 6.7.1 and the Laboratory Manual for details).

The following assessments and procedures should be performed within 28 days prior to the first dose of MEDI4736 monotherapy (Table 3), tremelimumab monotherapy (Table 4), MEDI4736+tremelimumab (Table 5) or Standard of Care (Table 8 for patients who will receive gemcitabine or vinorelbine and Table 9 for patients who will receive erlotinib). For details of the nature of the assessments, see below.

- Signed sub-study informed consent for the treatment period of the study
- Formal eligibility criteria verification
- Past medical and surgical history
- Details of any palliative radiotherapy
- Physical examination to assess all conditions that are current and ongoing
- Weight, height and vital signs: systolic blood pressure and diastolic blood pressure, pulse, respiratory rate, body temperature and oxygen saturation.
- Recording of AEs from the time of pre-screening consent

- Concomitant medications
- WHO performance status
- Haematology, clinical chemistry and urinalysis
- Coagulation tests: prothrombin time, activated partial thromboplastin time (APTT) and international normalised ratio (INR)
- Hepatitis B and C testing as per local practice
- HIV-1 antibody testing as per local practice
- Thyroid function tests: triiodothyronine (T3; free [if available]), total thyroxine (T4 [or T4 free]), and thyroid stimulating hormone (TSH)
- Pregnancy testing for female patients, as clinically indicated (urine human chorionic gonadotropin [hCG] or serum βhCG)
- 12-lead ECG recording
- Patient questionnaires (European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire [EORTC QLQ-C30] with the Lung Cancer Module [LC13] and EuroQoL 5-dimension, CCI [redacted]
- CCI [redacted]
- Tumour assessment scans of the chest and abdomen (including liver and adrenal glands) for assessment of disease by CT/MRI (see Appendix F).

Note: If Screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1.

The Principal Investigator/sub-investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

6.2.2 Follow-up procedures

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled, see Section 5.8. The assessments to be carried out during follow-up are detailed in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10 [follow-up for patients treated with Standard of Care]).

Any serious and/or non-serious AEs ongoing at the time of treatment discontinuation or which have occurred during the follow-up period must be followed-up (in accordance with Section 6.4.3 and Section 6.4.4). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF.

Every effort should be made to obtain accurate follow-up information on patients whose PFS and OS data were not accurately recorded. For example, in the case of PFS, the local investigator could provide their clinical assessment of progression if care transfers elsewhere, and for OS an effort should be made to continue to follow and use death registries where necessary.

6.2.2.1 Survival follow-up

Assessments for survival status should be made following confirmed objective disease progression (per RECIST v1.1) as presented in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab: Table 6 [follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10). No OS data will be recorded in the study database after final DCO for the study, but such information may continue to be collected for operational purposes for patients who remain eligible for re-treatment with study drug.

Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. In addition, patients should be contacted in the week following the DCO for the final analysis of OS for each sub-study, to provide complete survival data.

The status of patients ongoing in the study, those withdrawn (from the study) and those lost to follow-up at the time of an OS analysis should be obtained by the site personnel, by checking the patient notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient (ie, if the patient is dead or alive) can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

6.2.2.2 Second progression

Following objective progression, patients will be assessed every 12 weeks for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2.

The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

6.3 Efficacy

RECIST 1.1 criteria will be used to assess patient response to treatment and allow calculation of PFS, ORR, and DoR. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (CR, PR, SD or PD) are presented in Appendix F.

The same method of assessment of tumour burden used at baseline CT/MRI scans of the chest and abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment.

The baseline assessment should be performed within the 28 days prior to randomisation and ideally as close as possible before the start of study treatment. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks for the first 48 weeks (relative to the date of randomisation per Table 3 for MEDI4736 monotherapy, Table 4 for tremelimumab monotherapy, Table 5 for MEDI4736+tremelimumab, Table 8 for gemcitabine and vinorelbine and Table 9 for erlotinib), and then every 12 weeks thereafter, until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment and/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 study drug due to toxicity or a reason other than confirmed PD, objective tumour assessments should be continued every 8 weeks for 12 months/48 weeks (relative to the date of randomisation) then every 12 weeks thereafter until confirmed objective disease progression.

In the monotherapy arms, disease progression that occurs while on treatment requires confirmation. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with MEDI4736 monotherapy or tremelimumab monotherapy will continue between the initial assessment of progression and confirmation for progression. In the Standard of Care arm, it is at the investigator's discretion if a patient with uncertain PD continues treatment until PD is confirmed; however, a confirmatory scan is required for all patients in the Standard of Care arm even if a subsequent treatment is started.

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period will enter follow-up. When these patients experience evidence of PD, with or without confirmation, during follow-up and meet the criteria for treatment in the setting of PD, they will be given the option to restart their assigned immune-mediated cancer treatment (ie, MEDI4736 monotherapy or tremelimumab monotherapy) for as long as the investigator judges they are gaining clinical benefit with the same treatment guidelines followed during the initial 12-month treatment period. Patients should have a baseline tumour

assessment within 28 days prior to restarting their assigned immune-mediated cancer treatment; all further scans should occur every 8 weeks (relative to the date of restarting treatment) until study treatment is stopped. Only patients who the investigator determines do not have any significant, unacceptable, or irreversible toxicities, or would continue to receive benefit from therapy can restart treatment upon PD. Treatment will continue for as long as the investigator judges they are gaining clinical benefit. Only 1 retreatment cycle can occur.

In the MEDI4736+tremilimumab combination arm, retreatment can only occur if PD, with or without confirmation, occurs during the monotherapy portion or during the follow-up phase after completion of 12 months of treatment. During the retreatment period, the patient would resume MEDI4736 20 mg/kg Q4W as during the initial induction period, along with tremelimumab 1 mg/kg Q4W for 4 doses. Monotherapy with MEDI4736 10 mg/kg Q2W would then resume at Week 16, 4 weeks after the last dose of combination treatment, for as long as the investigator judges they are gaining clinical benefit.

Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug.

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

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

  The assessment of progression of ≥20% increase in the sum diameters of target lesions compared with the nadir is at the first progression time point relative to the nadir (the smallest sum of diameters and this may be at baseline or subsequent follow-up visit). The confirmed scan confirms the persistence of the ≥20% increase relative to the nadir.

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

- and/or additional new unequivocal lesions at the confirmatory PD time point compared with the first time point new lesions identified.

In the absence of clinically significant deterioration the investigator should continue the patient on the planned treatment schedule for the MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab arms until progression is confirmed. In the Standard of Care arm, it is at the investigator's discretion if a patient with uncertain PD continues treatment until PD is confirmed. In cases of unequivocal progression the investigator should discontinue treatment.

If progression is not confirmed then the patient should continue on study treatment and on treatment assessments.

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

Categorisation of objective tumour 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 tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR) and SD will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

Following confirmed progression, patients should continue to be followed up for survival every 2 months as outlined in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10) until final DCO. An exception would be those patients with confirmed PD during the initial treatment period that continue to receive study treatment at the discretion of the investigator (following consultation with the sponsor); these patients can receive treatment for a maximum of 12 months/48 weeks as applicable. Patients will have scans every 8 weeks (relative to the date of randomisation) until study treatment is stopped per Table 3, Table 4 and Table 5 (Screening and Treatment Period). Study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period). Retreatment may continue as long as the investigator judges the patient to be gaining clinical benefit.

Patients with confirmed PD that discontinue study treatment, should have scans conducted according to local standard clinical practice (see Section 6.2.2.2) until the patient commences a new treatment (these scans are optional; MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 10).

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans and Appendix F (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], respectively, and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 8 [vinorelbine or gemcitabine], Table 9 [erlotinib] and Table 10 [follow-up for patients treated with Standard of Care]).

Central reading of scans

Efficacy evaluation of PFS, ORR and DoR will be derived using investigator assessments according to RECIST 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside of visit windows) will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organisation to be stored and possibly used for a central review at a later stage. The management of patients will be based solely upon the results of the RECIST assessment conducted by the investigator.

6.4 Safety

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

Safety guidelines around SAE reporting described within the protocol remain in effect after the final DCO.

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, 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 SAEs and non-serious AEs.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected. Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an AE as far as the deterioration can be anticipated.

6.4.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, treatment, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from time of signature of the **sub-study** informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of MEDI4736 and/or tremelimumab and 30 days after the last dose of Standard of Care).

Adverse events not meeting SAE criteria that occur after the final DCO for the study will be followed up as per standard clinical practice but will not be recorded for the purposes of this study.

All SAEs will be recorded from the time of signature of the **pre-screening** informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of MEDI4736 and/or tremelimumab and 30 days after the last dose of Standard of Care). For SAEs that occur in the pre-screening period, additional information such as medical history may be requested.

After the final DCO, any SAEs occurring whilst the patient is either still receiving study drug (ie, re-treatment patients) or is in the 90-day safety follow-up period after receiving the last dose of study drug should be reported to AstraZeneca following the procedures outlined in Section 6.4.4. If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumour assessments using RECIST, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further RECIST assessments.

For screening failures (ie, patients who do not receive study treatment), SAEs will be collected from the time of signature of the **pre-screening** informed consent until the patient is withdrawn from the study. Any SAE related to a mandated study procedure should be reported.

Follow-up of unresolved adverse events

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

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca/MedImmune 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.

Post-study events

After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients after the 90-day/30-day safety follow-up period for patients in the MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab, and Standard of Care arms, respectively. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify AstraZeneca/MedImmune, Drug Safety or its representative.

Variables

The following variables will be collected for each AE on the eCRF:

- AE (verbatim)
- The date and time when the AE started and stopped
- The maximum CTCAE grade reported
- CTC grade changes for events of Grade 3 or above
- Whether the AE is serious or not
- Investigator causality rating against the study treatment (yes or no)
- Action taken with regard to study treatment
- Administration of treatment for the AE
- AE caused patient's withdrawal from study *(*yes or no*)*

- Outcome.

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

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 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The investigator will assess causal relationship between study treatment 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 study treatment?'

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Relationship to protocol procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes non-treatment-emergent SAEs (ie, SAEs that occur prior to the administration of study treatment) as well as 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/intervention that was described in the protocol for which there is no alternative aetiology present in the patient's medical record.

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

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.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised 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 fulfil any of the SAE criteria or are the reason for discontinuation of treatment. An abnormal laboratory finding (including ECG findings) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should also be reported as an AE.

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

Asymptomatic Grade 3 or 4 increases in amylase or lipase resulting in interruption of dosing (Refer to Section 5.5.3) should be reported as AEs.

Deterioration of a laboratory value, which 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.

Note**:** Cases where a patient shows an AST **or** ALT ≥3 × ULN **or** total bilirubin ≥2 × ULN may need to be reported as SAEs. 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 fulfil any of the SAE criteria. For potential Hy's Law to be met, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur. Please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions in cases of combined increases of aminotransferase and total bilirubin.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo

- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 × ULN, 1 or more also show elevation of serum total bilirubin to >2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

Guidelines for management of patients with hepatic function abnormality are outlined in the TMGs (Refer to Section 5.5.3).

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product 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, which are unequivocally due to disease progression, should not be reported as an AE during the study.

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.

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 the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as a SAE.

- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported to the study monitor as a 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 a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca/MedImmune Drug Safety or its representative within the usual timeframes.

6.4.4 Reporting of serious adverse events

All SAEs occurring whilst the patient is either still receiving study drug (ie, treatment or re-treatment patients) or is in the 90 day safety follow-up period after receiving the last dose of study drug have to be reported, whether or not considered causally related to study treatment, or to the study procedure(s). All SAEs occurring prior to the final DCO will be recorded in the eCRF. If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca/MedImmune representatives (ie, QuintilesIMS) immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

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

Investigators or other site personnel send relevant eCRF modules by fax to QuintilesIMS and any other relevant supporting documentation (eg, ECG, laboratory results, autopsy report).

Please refer to the study specific Safety Handling Plan. The AstraZeneca/MedImmune representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for MEDI4736 and the European Summary of Product Characteristics for the active Standard of Care products.

After the final DCO, any SAEs occurring whilst the patient is either still receiving study drug (ie, re-treatment patients) or is in the 90 day safety follow-up period after receiving the last dose of study drug are to be recorded in a paper CRF and reported directly to the AstraZeneca/MedImmune 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.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, urinalysis, thyroid function tests, amylase, and lipase will be taken at the times indicated in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 8 [vinorelbine or gemcitabine], Table 9 [erlotinib] and Table 10 [follow-up for patients treated with Standard of Care]). Please also refer to the Laboratory Manual.

Patients in progression-free follow-up after the final DCO are to undergo sampling for local laboratory assessments in such a way that continued per-protocol re-treatment eligibility can be properly determined. For patients receiving re-treatment after final DCO, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment with study drug in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3); data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

The laboratory variables to be measured are presented in Table 19, Table 20 and Table 21.

Table 19 Haematology

Activated partial thromboplastin time[a]	Mean corpuscular haemoglobin concentration
Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Haematocrit	Neutrophils
Haemoglobin	Platelet count
International normalised ratio	Red blood cell count
Lymphocytes	Total white cell count
Mean corpuscular haemoglobin	

[a] Activated partial thromboplastin time will be determined at Screening only, unless clinically indicated.
Haematology assessments (absolute counts, as appropriate) to be performed at each visit and when clinically indicated.

Table 20 Clinical chemistry (serum or plasma)

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

a Tests for aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin must be conducted concurrently and assessed concurrently.
b Gamma glutamyltransferase tested at Screening, Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1) and as clinically indicated.
c Creatinine clearance, magnesium**,** amylase, lipase, and uric acid tested at Screening, Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1) and every 4 weeks thereafter. In the MEDI4736+tremelimumab combination arm, amylase and lipase are tested at Screening, Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1) and every 4 weeks thereafter; creatinine clearance, magnesium, and uric acid are tested at Screening, Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1) and every 4 weeks until Week 12, and every 2 weeks thereafter. Amylase and lipase levels that do not meet the AE reporting criteria (see TMGs - Section 5.5.3) will not be captured.

Clinical chemistry assessments to be performed at each visit and when clinically indicated.

Note**:** In case a patient shows an AST **or** ALT ≥3 × ULN **or** total bilirubin ≥2 × ULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', 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 fulfil any of the SAE criteria. All patients with an AST, ALT or bilirubin value (the latter ≥1.5 x 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 (±7days) after permanent discontinuation of study treatment.

Table 21 Urinalysis[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

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

Urinalysis to be performed Screening, Day 1, every 4 weeks of study treatment and as clinically indicated.

Haematology, clinical chemistry and urinalysis tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. See Section 6.4.3 for when abnormal laboratory values should be reported as AEs.

All patients who have any CTC 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 CTC Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

For blood volumes see Section 7.1.

6.4.6 Physical examination

For timing of individual measurements refer to the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 8 [vinorelbine or gemcitabine], Table 9 [erlotinib] and Table 10 [follow-up for patients treated with Standard of Care]). Patients receiving re-treatment after final DCO are to undergo physical examinations as clinically indicated at the discretion of the investigator and per local standard of care; data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen,

skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems.

Performance status will be assessed using WHO performance status at the times specified in the study plans based on the following:

0 Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia.

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains patients who are fully active, as in Grade 0, but only with the aid of analgesics.

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

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

4 Completely disabled, unable to carry out any self-care and confined totally to bed or chair.

Note: WHO 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, please provide WHO performance status when information on subsequent anti-cancer therapy is provided, where possible.

6.4.7 ECG

Electrocardiograms will be analysed locally according to the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 8 [vinorelbine or gemcitabine],Table 9 [erlotinib] and Table 10 [follow-up for patients treated with Standard of Care]). Note for patients in the **MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab arms only**: On Day 1 and Week 12, mandatory ECGs should be recorded within 30 and 60 minutes before the start of the infusion and at least one time point 0 to 3 hours after the infusion (for the combination arm this is 0 to 3 hours after the second infusion).

Patients receiving re-treatment after final DCO are to receive ECGs as clinically indicated at the discretion of the investigator and per local standard of care; data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

Paper tracings will be used for local management, but a digital copy of all ECGs will be held centrally by a central ECG provider, and the data from this review will be stored for analysis if necessary at the end of the study. Two paper copies of each ECG should be printed (one copy can be provided to the central ECG core laboratory to be digitised and analysed if necessary). The independent review will not replace the local review by the investigator or cardiologist. Clinical interpretation and management of patients for all ECGs will be done locally.

The same method of assessment should be used throughout.

At Screening, digital ECGs should be performed in triplicate with a 2- to 5-minute time lag between each measurement. During treatment, only a single digital ECG measurement is required at each visit assessment. Additional ECGs will be performed when clinically indicated, eg, in the event of a cardiac AE. Triplicate ECGs should be performed to measure ECG intervals (eg, PR, QT, QRS, etc) if ECG abnormalities are being investigated.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. The investigator should record that the ECG has been clinically evaluated, but no interval data should be recorded on the eCRF.

Electrocardiograms will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF (see Section 6.4.3).

At Screening, mean QTc with Bazett's correction ($QTc = QT/\sqrt{R}$) must be <470 msec.

6.4.8 Vital signs

For timings of assessments refer to the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], respectively, and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 8 [vinorelbine or gemcitabine], Table 9 [erlotinib] and Table 10 [follow-up for patients treated with Standard of Care]). Patients receiving re-treatment after final DCO are to undergo vital signs assessments as clinically indicated at the discretion of the investigator and per local standard of care; data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

Patients in the MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab arms will be monitored with assessment of vital signs (blood pressure, pulse, respiratory rate, temperature and oxygen saturation) at Screening and on the day of each infusion and in the follow-up period on Day 30. On infusion days, vital signs will

all be taken before the infusion. Blood pressure and pulse will also be collected during and after the infusion (see Section 6.4.8.1).

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

Additional recording of vital signs may be captured on an unscheduled vital signs eCRF and on the eCRF for AE/SAE where applicable. The date and time of collection and measurement will be recorded on the appropriate eCRF.

For patients in the Standard of Care arm, vital signs should be taken in line with local practice guidelines. In addition, for patients receiving gemcitabine and vinorelbine, please provide vital signs measurements at the beginning and end of each infusion where possible.

6.4.8.1 Pulse and blood pressure

Patients in the MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab arms will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- Every 15 minutes during the infusion (at 15, 30 and 45 minutes) (all ±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1-hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes)

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

For the combination arm these assessments should be followed for each of the 2 component infusions.

The date and time of collection and measurement will be recorded on the appropriate eCRF.

6.4.8.2 Temperature, respiratory rate and oxygen saturation

On infusion days, temperature, respiratory rate and oxygen saturation should be collected before the infusion.

6.4.9 Other safety assessments

Pregnancy tests on either blood (serum β-hCG) or urine (hCG) samples will be performed for pre-menopausal women of childbearing potential at the times specified in Table 3 (MEDI4736), Table 4 (tremelimumab monotherapy), Table 5 (MEDI4736+tremelimumab), Table 8 (vinorelbine or gemcitabine), and Table 9 (erlotinib). Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

Other safety tests to be performed at Screening include:

- Coagulation tests: prothrombin time, APTT and INR. Prothrombin time, APTT and INR only performed at Screening unless clinically indicated.
- Hepatitis B and C testing as per local practice
- HIV-1 antibody testing as per local practice
- T3 free (if available), total T4 (or T4 free), and TSH.

Timings for additional thyroid function tests in the MEDI4736 arm (TSH and T3 free [if available] and total T4 [or T4 free]) are shown in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]).

6.5 Patient reported outcomes

Timings of the assessments for PRO are presented in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 8 [vinorelbine or gemcitabine], Table 9 [erlotinib] and Table 10 [follow-up for patients treated with Standard of Care]). There will be no further collection of PRO data after the final DCO for the study.

The EORTC QLQ-C30 and cancer-specific symptom modules are self-administered questionnaires and are to be completed by the patient without the assistance of the investigational site personnel. All questionnaires should be completed before any other study procedures are conducted at the visit. Patient reported outcome questionnaires need to be administered at the times specified in the study plans before other clinical procedures. If patients have scans at an outside facility or missed a scheduled data collection, PRO questionnaires need to be administered at the next visit. It takes about 20 to 40 minutes for

patients to complete all 3 questionnaires and the patients are asked to only fill out questionnaires that have been validated to be relevant to their specific type of cancer; hence the burden to the patient is moderate. When the patient completes the questionnaires, study coordinators need to review the questionnaires for missing responses and then ask the patient to date and sign at places specified in the questionnaires.

6.5.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item self-administered questionnaire (Appendix G). There are 9 multiple item scales: 5 scales that assess aspects of functioning (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health status/Quality of Life (QoL) scale. There are 5 single-item measures assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea) and a single item concerning perceived financial impact of the disease. All but 2 questions have 4-point scales: "Not at all," "A little," "Quite a bit," and "Very much." The 2 questions concerning global health status and QoL have 7 point scales with ratings ranging from "Very poor" to "Excellent." For each of the 15 domains (9 multiple-item scales, 6 single item scales), final scores are transformed such that they range from 0 to 100 where as higher scores indicate greater functioning, greater QoL, or greater level of symptoms (Aaronson et al 1993).

6.5.2 Lung Cancer Module

For NSCLC patients, a disease-specific 13-item self-administered questionnaire for lung cancer was developed (LC13; Appendix G) 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, haemoptysis, dyspnoea, and pain) and side effects from conventional chemotherapy and radiotherapy (ie, hair loss, neuropathy, sore mouth and dysphagia). The EORTC QLQ-C30 questionnaire should be completed before the LC13 module.

6.5.3 EuroQoL 5-dimension, CCI [redacted]

The EuroQoL 5-dimension utility index (EQ-5D; Appendix G) is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQoL 2013).

CCI [redacted]

CCI

[redacted]

6.5.4 Administration of patient reported outcomes questionnaires

Each centre must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse, study coordinator) and if possible, assign a back-up person to cover if that individual is absent. The AstraZeneca/MedImmune Study Delivery Team (or delegate) will provide relevant training in the administration of the PRO questionnaires. The PRO questionnaires must be administered and completed at the clinic as per the study plan. The EORTC-QLQC 30, LC13, and EQ-5D will be administered on the days specified in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]; Standard of Care: Table 8 [vinorelbine or gemcitabine], Table 9 [erlotinib] and Table 10 [follow-up for patients treated with Standard of Care]).

It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- It must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions
- It must be completed in private by the patient
- The patient should be given sufficient time to complete the PRO questionnaires at their own speed

- The patient should not receive help from relatives, friends or clinic staff to answer the PRO questionnaires. However, if the patient is unable to read the questionnaire (eg, is blind, illiterate, or forgot their reading glasses), the PRO questionnaires may be read out by trained clinic staff and responses recorded.

- On completion of the PRO questionnaires, it should be handed back to the person responsible for PRO questionnaires, who should check for completeness

- Only 1 answer should be recorded for each question

- Data from the paper questionnaires will be transcribed at the investigator site onto the eCRF.

6.5.5 Patient interviews (optional)

CCI

[redacted]

CCI [redacted]

6.6 Pharmacokinetics and ADA (MEDI4736, tremelimumab and MEDI4736+tremelimumab arms only)

6.6.1 Collection of PK samples and determination of drug concentration

Blood samples (3.5 mL) for determination of MEDI4736 and tremelimumab in serum will be taken at the times presented in the study plans (MEDI4736 monotherapy, tremelimumab monotherapy or MEDI4736+tremelimumab: Table 3, Table 4 or Table 5 [Screening and Treatment Period], and Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 7 [for follow-up of patients discontinuing due to confirmed PD]. Patients receiving re-treatment after final DCO will not undergo drug concentration or anti-drug antibody assessments.

Measurement of MEDI4736 and tremelimumab concentrations in serum will be performed using a validated immunoassay. Samples for determination of MEDI4736 and tremelimumab concentrations in serum will be analysed by a designated third party on behalf of AstraZeneca/MedImmune, using an electrochemiluminescence and ELISA assay, respectively. The lower limit of quantification in serum is 50 ng/mL (MEDI4736) and 156 ng/mL (tremelimumab) and may be modified if needed and justified.

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual. For blood volume see Section 7.1.

6.6.2 Collection of samples to measure for the presence of ADA and ADA neutralising antibodies

Presence of ADA will be assessed in samples (from patients in the MEDI4736 monotherapy, tremelimumab monotherapy and MEDI4736+tremelimumab arms only) taken according to the schedule presented in Table 3, Table 4 and Table 5 (Screening and the Treatment Period), Table 6 (for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 7 (for follow-up of patients discontinuing due to confirmed PD).

Samples will be measured for the presence of ADA and ADA neutralising antibodies using validated assays. Tiered analysis will be performed to include screening, confirmatory and

titre assay components and positive-negative cut points will be employed that were statistically determined from drug naive validation samples.

6.7 Biomarker analysis

CCI

[redacted]

6.7.1 Collection of PD-L1 expression data for sub-study assignment

At Pre-screening, there is 1 mandatory provision of tissue to be used for determination of eligibility:

Note: If the patient's PD-L1 status has already been assessed using the analytically validated Ventana assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

- MANDATORY: Provision of a newly acquired tumour sample (preferred) OR archival tissue obtained within 3 years. ONLY 1 sample (either newly acquired or archival tissue) will be used to assess PD-L1 status for purposes of eligibility. Where multiple samples have been submitted for the same patient, results from the most recent evaluable sample will inform patient status for eligibility.

- Samples should be collected via a core needle of 18 gauge or larger or be collected as an excisional tumour biopsy sample. Where institutional practice, in this setting, uses a

smaller gauge needle, samples should be submitted in sufficient number to ensure that a valid result can be achieved.

- When tissue is newly obtained using an 18-gauge needle 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 Pathology Manual. When a smaller gauge needle is used, the number of cores rises to 3 or 4.

- The tumour specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC analysis (see the Pathology Manual).

- Samples with limited tumour content and fine needle aspirates are inadequate for defining tumour PD-L1 status.

Tumour lesions used for newly acquired biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy.

If a RECIST 1.1 target lesion is used for biopsy, the lesion must be ≥2 cm in the longest diameter and must be biopsied outside of the screening period.

- OPTIONAL: The collection of additional archived tumour tissue block (formalin-fixed paraffin-embedded) is highly encouraged, where such samples exist in a quantity sufficient to allow for analysis. This specimen may be supplied at any time during the study. Tumour tissue block is preferred. If a tissue block is unavailable, 10-15 unstained slides with tissue sections of 4 microns thick may be submitted. Please consult the Laboratory Manual for specific instructions and guidelines regarding sections.

- OPTIONAL: The collection of additional biopsies prior to re-treatment, if feasible, or clinically indicated is strongly encouraged.

Additional tumour biopsies collected as part of clinical care (eg, for mixed responses or upon PD) can be submitted for further analysis.

Please review the Laboratory Manual for additional details.

The sponsor intends to assign patients to Sub-study A or B according to their PD-L1 expression status. Tumour biopsies will be stored at AstraZeneca/MedImmune Research and Development (R&D) or an appropriate vendor selected by AstraZeneca/MedImmune. Core biopsies may be used for correlative studies such as immunohistochemistry, tumour mutation analysis, RNA analysis, proteomic analysis, and assessment of immunodiversity. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Testing will be completed on either a recent tissue biopsy or an archival sample (see Inclusion Criterion 6 in Section 4.1) prior to randomisation using a validated Ventana assay (details will be provided in the Investigator's Laboratory Manual). The Ventana PD-L1

immunohistochemistry assay will be used to determine PD-L1 immunohistochemistry status in this study.

In patients where both archived (≤3 years) and newly acquired samples are available, both samples will be analysed to gain understanding about the relationship between these samples, co-evolution of a patient's tumour and immune system, and to help determine which sample type may have the greatest utility for predicting response to therapy. If both samples are submitted prior to sub-study assignment, the PD-L1 result from the most recently acquired sample will always take precedence in sub-study assignment unless such sample is unevaluable or unavailable. In the event that a sample is unevaluable or unavailable, the other sample can be used for sub-study assignment. Optional, additional archived samples >3 years will be used for exploratory analysis only and not for PD-L1 determination and sub-study assignment.

In addition, if it is feasible, tumour biopsies are to be taken upon disease progression after randomisation to study treatment. Based on the number and viability of the samples collected, we will assess whether there is any correlation between PD-L1 expression and response to treatment.

6.7.2 Collection of exploratory biomarker data

6.7.2.1 Blood borne biomarkers

CCI [redacted]

6.7.2.2 Tumour samples

CCI [redacted]

6.7.2.3 Genomic analysis

CCI [redacted]

6.7.3 Management of exploratory biomarker data

CCI [redacted]

[redacted]

6.8 Pharmacogenetics

CCI [redacted]

6.9 Health economics

For the purposes of economic evaluation it is necessary to capture healthcare resource use related to the treatment and the underlying disease. Within the study the following will be captured:

- Hospital episodes including the type of contact (hospitalisations, outpatient, day case), reason, length of stay by ward type (including intensive care unit) and concomitant medications and procedures
- Treatment related to AEs (including the method of delivery of the treatment)
- Treatment not related to the study.

The above resource use data will mainly come from the patient's medical record and will be captured in the eCRF.

The assessment of health economic resource use data will provide important information for payers and will be used within economic evaluations of MEDI4736.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study depends on the length of time that the patient receives study treatment. Table 22 (MEDI4736), Table 23 (tremelimumab), Table 24 (MEDI4736+tremelimumab) and Table 25 (Standard of Care) are a guide to the approximate volume of blood that will be drawn from each patient, based on the assumption that each patient remains in the study on treatment for 3 months and attends all the planned visits. The sample volumes below are intended as a guide, the exact volume will be dependent on the collection tube sizes available from the supplier (eg, site, Contract Research Organisation).

Blood samples taken during progression-free follow-up or during re-treatment following the final DCO are to be in accordance with the investigator's judgment and local institutional practice.

Laboratory assessments for patients in progression-free follow-up after final DCO should be monitored in such a way that continued per-protocol re-treatment eligibility can be properly determined. For patients receiving re-treatment after final DCO, it is recommended that investigators monitor the patient's safety laboratory assessments prior to and periodically during treatment in order to manage AEs in accordance with the toxicity management guidelines (Refer to Section 5.5.3).

Table 22 Volume of blood to be drawn from each patient in the MEDI4736 monotherapy arm (Sub-study A and B) in the first 3 months on treatment

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (serum chemistry)	1.0	8	**8.0**
	Haematology	2.0	8	**16.0**
	Hepatitis/HIV	3.0	1	**3.0**
	Thyroid	1.0	5	**5.0**
	Coagulation	3.0	1	**3.0**
Pharmacokinetic(s)		3.5	3	**10.5**
ADA testing including ADA neutralising antibodies (to identify ADA responses in patient circulation)		8.5 (1 x 3.5 mL sample for NAb and 1 x 5.0 mL sample for ADA)	2	**17.0**
CCI				
Pharmacogenetic(s)		8.5	1	**8.5**
Total MEDI4736 monotherapy		**46.5 mL**	**36**	**100.5 mL**

ADA Anti-drug antibody; HIV Human immunodeficiency virus; miRNA Micro RNA; mRNA Messenger RNA; NAb Neutralising antibodies; PD-L1 Programmed death ligand 1.

Table 23 Volume of blood to be drawn from each patient in the tremelimumab monotherapy arm (Sub-study B) in the first 3 months on treatment

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (serum chemistry)	1.0	5	**5.0**
	Haematology	2.0	5	**10.0**
	Hepatitis/HIV	3.0	1	**3.0**
	Thyroid	1.0	5	**5.0**
	Coagulation	3.0	1	**3.0**
Pharmacokinetic(s) for tremelimumab		3.5	3	**10.5**
ADA testing including ADA neutralising antibodies (to identify ADA responses in patient circulation) for tremelimumab		8.5 (1 x 3.5 mL sample for NAb and 1 x 5.0 mL sample for ADA)	2	**17.0**
CCI				
Pharmacogenetic(s)		8.5	1	**8.5**
Total tremelimumab arm		**46.5 mL**	**30**	**91.5 mL**

ADA Anti-drug antibody; HIV Human immunodeficiency virus; miRNA Micro RNA; mRNA Messenger RNA; NAb Neutralising antibodies; PD-L1 Programmed death ligand 1.

Table 24 Volume of blood to be drawn from each patient in the MEDI4736+tremelimumab arm (Sub-study B) in the first 3 months on treatment

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (serum chemistry)	1.0	5	**5.0**
	Haematology	2.0	5	**10.0**
	Hepatitis/HIV	3.0	1	**3.0**
	Thyroid	1.0	5	**5.0**
	Coagulation	3.0	1	**3.0**
Pharmacokinetic(s) for MEDI4736		3.5	3	**10.5**
Pharmacokinetic(s) for tremelimumab		3.5	3	**10.5**
ADA testing including ADA neutralising antibodies (to identify ADA responses in patient circulation) for MEDI4736		8.5 (1 x 3.5 mL sample for NAb and 1 x 5.0 mL sample for ADA)	2	**17.0**
ADA testing including ADA neutralising antibodies (to identify ADA responses in patient circulation) for tremelimumab		8.5 (1 x 3.5 mL sample for NAb and 1 x 5.0 mL sample for ADA)	2	**17.0**
CCI [redacted]				
Pharmacogenetic(s)		8.5	1	**8.5**
Total MEDI4736+**tremelimumab arm**		**58.5 mL**	**35**	**119 mL**

ADA Anti-drug antibody; HIV Human immunodeficiency virus; miRNA Micro RNA; mRNA Messenger RNA; NAb Neutralising antibodies; PD-L1 Programmed death ligand 1.

Table 25 Volume of blood to be drawn from each patient in the Standard of Care arms in the first 3 months on treatment

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (serum chemistry [**gemcitabine and vinorelbine**])	1.0	8	**8.0**
	Clinical chemistry (serum chemistry [**erlotinib**])	1.0	5	**5.0**
	Haematology (**gemcitabine only**)	2.0	11	**22.0**
	Haematology (**vinorelbine only**)	2.0	14	**28.0**
	Haematology (**erlotinib only**)	2.0	5	**10.0**
	Hepatitis/HIV	3.0	1	**3.0**
	Coagulation	3.0	1	**15.0**
	Thyroid	1.0	1	**1.0**
CCI [redacted]				
Pharmacogenetic(s)		8.5	1	**8.5**
Total for patients treated with erlotinib		**34.5 mL**	**21**	**72.0 mL**
Total for patients treated with gemcitabine		**34.5 mL**	**30**	**87.0 mL**
Total for patients treated with vinorelbine		**34.5 mL**	**33**	**93.0 mL**

HIV Human immunodeficiency virus; miRNA Micro RNA; mRNA Messenger RNA; PD-L1 Programmed death ligand 1.

7.2 Handling, storage and destruction of biological samples

CCI [redacted]

CCI [redacted]

AstraZeneca/MedImmune ensures that any biological samples remaining after analysis have been performed may be repatriated upon request or kept until the end of the period specified in the informed consent.

7.2.1 Pharmacokinetic, immunogenicity and/or pharmacodynamic (soluble PD-L1) samples

Samples will be archived for a minimum of 5 years after the Biologic License Application. For sample processing, handling and shipment refer to the Investigators Laboratory Manual.

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. CCI [redacted] Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

CCI [redacted]

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca/MedImmune and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

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

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

QuintilesIMS keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 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/destroyed, and the action documented. If samples are already analysed, AstraZeneca/MedImmune is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The Principal Investigator:

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

AstraZeneca/MedImmune or its representative ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca/MedImmune will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

AstraZeneca/MedImmune ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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 Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

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

Extra precautions are taken to preserve confidentiality and prevent genetic data 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/MedImmune Physician (or representative or delegate) or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory Authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

CCI [redacted]

8.3 Ethics and regulatory review

An Ethics Committee (Independent Ethics Committee or Institutional Review Board [IRB], as applicable) should approve the final study protocol, including the final version of the Informed Consent Form 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 Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

For all countries except the US and Canada, AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

For the US and Canada, each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any SUSARs from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

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

The PGx component of the study (relating to DNA) is optional and will be detailed on a separate informed consent form.

Patients will sign a Pre-screening Informed Consent Form before any study procedure is conducted; this form will detail the pre-screening/screening assessments. Once the patient is assigned to either Sub-study A or B (depending on their PD-L1 status), they will be asked to sign the relevant Sub-study Informed Consent Form.

In the MEDI4736 and tremelimumab monotherapy arms, study drug should be discontinued if there is confirmed PD while on treatment following a previous response (PR or CR) to study

drug while on treatment (ie, the response and progression events both occurred while receiving study drug during the same treatment period).

For patients who receive study treatment through disease progression and patients who achieve disease control (ie, CR, PR or SD) and restart treatment, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient must meet the inclusion and exclusion criteria specified in Section 4.3. The informed consent documents will specify that treatment beyond initial evidence of PD or re-treatment for progression during follow-up is not the standard of care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue with treatment.

Patients who are eligible for re-treatment following final DCO must sign the re-treatment informed consent prior to receiving study drug. Copies of the informed consent must be maintained with the patient's medical records.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating 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 Ethics Committee and if applicable, also the national regulatory authority approval, 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(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

QuintilesIMS is responsible for the management of this study and thus throughout this section QuintilesIMS is considered the representative of AstraZeneca.

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures (including those listed in the Laboratory Manual) and the IVRS and WBDC system(s) utilised.

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.

9.3 Monitoring of the study

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

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

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

Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

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

Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

The study will continue until the last patient completes 90 days of follow-up after re-treatment or the last patient discontinues for any reason from the progression-free follow-up (so no further patients are eligible for re-treatment).

In the event that a roll-over or safety extension study will become available, patients currently receiving treatment with study drug or patients in progression-free follow-up may be transitioned to such a study, and the current study would end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any patient that would be proposed to move to such study would be asked to sign a new informed consent.

The study is expected to start in Q1 2015 and to end by Q4 2018.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, if recruitment is slow, or when there are no longer any patients being treated or followed in progression-free follow-up once the DCO for final OS analysis has occurred. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with MEDI4736.

9.5.1 Treatment after final Overall Survival data cut-off

The 2 sub-studies A and B are considered independent and may or may not be reported at the same time. At the time of final analysis, the clinical study database will be closed to new data.

Patients in OS follow-up (progressed and have completed treatment) will be considered to have completed the study. Patients in progression-free follow-up (patients who have completed study drug treatment and have not progressed and who are still potentially eligible for re-treatment) may decide to continue in the study in progression-free follow-up. These patients would therefore remain eligible for possible future re-treatment upon progression if they meet re-treatment criteria and the investigator judges that the patient will gain clinical benefit.

Patients who are receiving treatment at the time of final DCO may continue receiving investigational product if the investigator judges that they are gaining clinical benefit.

All patients will receive scans and follow-up care in accordance with standard local clinical practice. Patients in progression-free follow-up after the final DCO are to undergo sampling for local laboratory assessments in such a way that continued per-protocol re-treatment eligibility can be properly determined in the event of progression. For patients receiving re-treatment after final DCO, 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 in order to manage AEs in accordance with the toxicity management

guidelines (Refer to Section 5.5.3). All data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

For patients who do continue to receive treatment beyond the time of the final DCO, investigators will report SAEs to AstraZeneca/Medimmune Patient Safety via paper CRFs until 90 days after the last dose of study treatment (30 days for the Standard of Care arms), in accordance with Section 6.4.4 (Reporting of serious adverse events). Any non-serious AE that is ongoing at the time of this DCO is to be followed up at the discretion of the investigator and per local practice and in alignment with the toxicity management guidelines in Section 5.5.3 of this protocol. Data will not be captured for the purposes of this study outside of being recorded in the patients' source documents.

Following the final DCO, SAE reporting applies only to patients who are active on the drug and within 90 days post the last dose; in all other cases only a statement of death notification is to be sent to QuintilesIMS. No OS data will be recorded in the study database after final DCO for the study, but such information may continue to be collected for operational purposes for patients who remain eligible for re-treatment with study drug.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by QuintilesIMS.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by QuintilesIMS.

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.

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

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

Any genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure

system within AstraZeneca and/or third party contracted to work with AstraZeneca/MedImmune to analyse 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.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA, OR DELEGATE

A comprehensive Statistical Analysis Plan (SAP) will be prepared before the first patient is entered.

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 RECIST 1.1-based endpoints

All RECIST 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 anti-cancer 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 randomisation. If a patient has had a tumour 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).

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

11.1.2 Co-primary endpoints

Within Sub-study A and Sub-study B, the co-primary endpoints are OS and PFS.

11.1.2.1 Overall survival

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

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the

patient can be obtained by site personnel from publicly-available resources where it is possible to do so under applicable local laws.

11.1.2.2 Progression free survival

Progression free survival (per RECIST 1.1 as assessed by the investigator) will be defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer 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 Day 1 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 RECIST 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.

In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study treatment until progression has been confirmed.

11.1.3 Proportion of patients alive at 12 months (OS12)

The proportion of patients alive at 12 months will be defined as the Kaplan-Meier estimate of OS at 12 months.

11.1.4 Objective response rate

Objective response rate (per RECIST 1.1 as assessed by the investigator) is defined as the number (%) of patients with at least 1 visit response of CR or PR and will be based on a subset of all randomised patients with measurable disease at baseline per the site investigator (ie, the ITT population). 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.

11.1.5 Duration of response

Duration of response (per RECIST 1.1 as assessed by the investigator) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

The 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.

Duration of response will not be defined for those patients who do not have documented response.

11.1.6 Proportion of patients alive and progression free at 6 months

The proportion of patients alive and progression free at 6 months (ie, APF6) will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by the investigator) at 6 months.

11.1.7 Proportion of patients alive and progression free at 12 months

The proportion of patients alive and progression free at 12 months (ie, APF12) will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by the investigator) at 12 months.

11.1.8 Time from randomisation to second progression (PFS2)

PFS2 will be defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the PFS endpoint or death. The date of the first progression will be programmatically determined from investigator assessed data (see Section 11.1.2.2 for details.) The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death. Second progression status will be reviewed every 12 weeks following the progression event used for the co-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, ie, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Adverse events

Data from all cycles of randomised 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 and treatment arm.

Any AE occurring before treatment with MEDI4736, tremelimumab, MEDI4736+tremelimumab or Standard of Care will be included in the data listings but will not be included in the summary tables of AEs.

Adverse events observed up until 90 days following discontinuation of the immunotherapy agents (ie, the last dose of MEDI4736, tremelimumab or MEDI4736+tremelimumab)/30 days following discontinuation of the Standard of Care agent or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only as a number of AEs up to 90 days following discontinuation of the immunotherapy agents/30 days following discontinuation of the Standard of Care agent are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of the immunotherapy agents/30 days following discontinuation of the Standard of Care agent (ie, without taking subsequent therapy into account). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of the immunotherapy agents (MEDI4736, tremelimumab or MEDI4736+tremelimumab) or more than 30 days after discontinuation of the Standard of Care agent will be produced. These events will not be included in AE summaries.

11.2.2 Other significant adverse events (OAEs)

During the evaluation of the AE data, an AstraZeneca/MedImmune 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 judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered 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 haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

11.2.3 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.

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)] × 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.

11.3 Calculation or derivation of patient reported outcome variables

PRO questionnaires will be assessed using the EORTC QLQ-C30 with the LC13 module (HRQoL with lung cancer specific additional concerns) and EQ-5D-5L. 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 ITT study population, unless stated.

11.3.1.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea/vomiting), 5 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea) 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 1999). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, 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.

The change from baseline in HRQoL will be assessed using the EORTC QLQ-C30 global QoL scale, which includes 2 items from the EORTC QLQ-C30: "How would you rate your overall health during the past week? (Item 29) and "How would you rate your overall QoL during the past week? (Item 30).

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales/items from the EORTC QLQ-C30 (OPDIVO® prescribing information). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorised as improvement, no change or deterioration as shown in Table 26.

Table 26 Mean change and visit response in health related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-C30 Global quality of life score	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom scales/items	≥+10	Deterioration
	≤-10	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire.

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 1999). 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 minimised.

Time to symptom deterioration

For each of the symptoms scales/items in the EORTC QLQ-C30, time to symptom deterioration will be defined as the time from randomisation until the date of the

first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) 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 anti-cancer therapy prior to symptom deterioration. 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 EORTC QLQ-C30) 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 Day 1. The population for the analysis of time to symptom deterioration will include a subset of the ITT population who have baseline scores of ≤90.

Time to QoL/Function deterioration

For QoL, time to deterioration will be defined as the time from the date of randomisation until the date of the first clinically meaningful deterioration (a decrease in the function scales or the global health status/QoL from baseline of ≥10) 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 anti-cancer therapy prior to QoL/function deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the QoL/function change could be evaluated.

Patients whose QoL (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 QoL/function could be evaluated. Also, if QoL deteriorates 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 QoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at Day 1. The population for the analysis of time to QoL/function deterioration will include a subset of the ITT population who have baseline scores of ≥10.

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 (a decrease from baseline score ≥10 for EORTC QLQ-C30 symptom scales/items) in that symptom from baseline. The denominator will consist of a subset of the ITT population who have a baseline symptom score ≥10.

QoL/function improvement rate

The QoL/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 (an increase from baseline score ≥10 for EORTC QLQ-C30 functional scales and global health status/QoL) in that scale from baseline. The denominator will consist of a subset of the ITT population who have a baseline QoL/function score ≤90.

11.3.1.2 Lung cancer module 13

The LC13 is a lung cancer specific module from the EORTC comprising 13 questions to assess lung cancer symptoms (cough, haemoptysis, dyspnoea and site-specific pain), treatment-related side-effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication.

The LC13 incorporates symptom scales including:

- Dyspnoea (multi-item scale based on 3 questions: were you short of breath when you rested; walked; climbed stairs)
- Cough: 1 item (how much did you cough?)
- Haemoptysis: 1 item (did you cough up blood?)
- Pain: 3 individual items (Have you had pain in your chest; your arm or shoulder; other parts of your body?)

The dyspnoea 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 LC13 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales/items from the LC13 (Osoba et al 1998). For example, a clinically meaningful deterioration or worsening in chest pain (as assessed by LC13) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful improvement is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in

symptoms from baseline will be categorised as an improvement, no change or deterioration as shown in Table 27.

Table 27 Visit Response for HRQoL and disease-related symptoms

Score	Change from baseline	Visit response
LC13 symptom scales/items	≥+10	Deterioration
	≤-10	Improvement
	Otherwise	No change

HRQoL Health Related Quality of Life; LC13 Lung Cancer Module.

Time to symptom deterioration

For each of the symptoms scales/items in LC13, time to symptom deterioration will be defined as the time from the date of randomisation until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) 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 anti-cancer therapy prior to symptom deterioration. 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 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 Day 1. The population for the analysis of time to symptom deterioration will include a subset of the ITT population who have baseline scores of ≤90.

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 (a decrease from baseline score ≥10 for LC13 symptom scales/items) in that symptom from baseline. The denominator will consist of a subset of the ITT population who have a baseline symptom score ≥10.

11.3.1.3 Calculation or derivation of health state utility (EQ-5D-5L)

CCI

[redacted]

CCI [redacted]

11.4 Calculation or derivation of pharmacokinetic variables

11.4.1 PK non-compartmental analysis

The PK sample analyses will be performed at AstraZeneca/MedImmune R&D. The actual sampling times will be used in the PK calculations. Pharmacokinetic concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated and included in the report. Pharmacokinetic parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined after the first or steady-state dose: peak and trough concentrations (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

11.4.2 Population PK and exposure-response/safety analysis

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

11.4.3 Immunogenicity analysis

Immunogenicity results will be reported descriptively by summarizing the number and percentage of patients who develop detectable anti-MEDI4736 and/or anti-tremelimumab antibodies. The immunogenicity titre and presence of neutralizing ADA will be reported for samples confirmed positive for the presence of anti-MEDI4736 antibodies and/or anti-tremelimumab antibodies. The effect of immunogenicity on PK, PDx, efficacy and safety will be evaluated if data allow.

11.5 Calculation or derivation of biomarker variable(s)

CCI [redacted]

11.6 Calculation or derivation of pharmacogenetic variables

In the case of genetic data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database,

which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (please see Appendix D).

11.7 Calculation or derivation of health economic variables

Frequency and estimates of resource use, including length of stay and number of hospital admissions, will be derived from the health resource use information.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

The 2 sub-studies A and B are considered independent and may or may not be reported at the same time. At the time of final analysis, the clinical study database will be closed to new data.

12.1 Description of analysis sets

A comprehensive SAP will be prepared and finalised before first patient in. The Full Analysis Set (FAS) and the Safety Analysis Set described below will be applied to all randomised patients in each of Sub-study A and Sub-study B.

Table 28 gives a summary of outcome variables and analysis populations.

Table 28 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
OS, PFS	ITT (FAS)
OS12, ORR, DoR, APF6, APF12, PFS2, PRO endpoints	ITT (FAS)
Demography	ITT (FAS)
PK data	PK
Safety data	
Exposure	Safety
Adverse events	Safety
Laboratory measurements	Safety
Vital Signs	Safety

APF6 Proportion of patients alive and progression free at 6 months from randomisation; APF12 Proportion of patients alive and progression free at 12 months from randomisation; DoR Duration of response; ITT Intent-to-Treat; ORR Objective response rate; OS Overall survival; OS12 Proportion of patients alive at 12 months from randomisation; PFS Progression free survival; PFS2 Time from randomisation to second progression; PK Pharmacokinetic; PRO Patient reported outcomes.

12.1.1 Full analysis set

The FAS will include all randomised patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive treatment are included in the FAS. The analysis of data using the FAS therefore follows the principles of ITT. Therefore, all efficacy and HRQoL data will be summarised and analysed using the FAS on an ITT basis.

12.1.2 Safety analysis set

All patients who received at least 1 dose of randomised treatment in each of the sub-studies will be included in the safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomised to Treatment A but actually given Treatment B) will be accounted for in the actual treatment arm.

When assessing safety and tolerability, summaries will be produced based on the safety analysis set.

12.1.3 PK analysis set

All patients who receive at least 1 dose of MEDI4736 (Sub-study A), or either MEDI4736+tremelimumab, MEDI4736 monotherapy or tremelimumab monotherapy (Sub-study B) per the protocol, for whom any post-dose data are available will be included in the PK analysis set. The population will be defined by the Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

12.2 Methods of statistical analyses

Sub-study A has 1 treatment comparison of interest as follows:

- MEDI4736 10 mg/kg Q2W compared with Standard of Care

Sub-study B has 1 treatment comparison of interest that is considered primary as follows:

- MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg Q4W for 12 weeks then MEDI4736 10 mg/kg Q2W for 34 weeks compared with Standard of Care

The co-primary endpoints in each of the sub-studies are OS and PFS using RECIST v1.1. The study was sized to assess PFS and OS endpoints in each of the sub-studies A and B for the treatment comparisons mentioned above. No hypothesis testing will be performed on OS and PFS in the PD-L1-positive population in Sub-study A.

The final analyses of OS will take place on Sub-study B on a pre-specified date when approximately 205 deaths have occurred from 300 patients (68% maturity) who have been randomised to the MEDI4736+tremelimumab and Standard of Care arms in Sub-study B. An interim analysis of OS for the primary treatment comparison (Section 12.2.14) will be performed for Sub-study B at the same time as the primary PFS analysis. However, for practical considerations, if it happens that the analysis time points for the final PFS and OS

analyses are closely aligned based on the occurrences of the events, then 1 single analysis of OS will be conducted along with the PFS analysis. In this case, the entire 0.04 alpha will be utilized for this OS analysis.

The final analyses of PFS and OS interim analysis will take place for Sub-study B on a pre-specified date when it is predicted that approximately 244 PFS events from 300 patients (81% maturity) who have been randomised to the MEDI4736+tremelimumab and Standard of Care arms.

Sub-study B has the following treatment comparisons of interest that are considered secondary:

1. MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg Q4W for 12 weeks then MEDI4736 10 mg/kg Q2W for 34 weeks compared with MEDI4736 10 mg/kg Q2W

2. MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg Q4W for 12 weeks then MEDI4736 10 mg/kg Q2W for 34 weeks compared with tremelimumab 10 mg/kg Q4W for 24 weeks then Q12W

3. MEDI4736 10 mg/kg Q2W compared with Standard of Care

4. Tremelimumab 10 mg/kg Q4W for 24 weeks then Q12W compared with Standard of Care

A contribution of components analysis will be performed for superiority analysing PFS for both of the secondary treatment comparisons ‘1’ and ‘2’ above. This analysis is planned to be performed when approximately 158 PFS events are observed in the MEDI4736+tremelimumab and tremelimumab monotherapy arms. However, for practical considerations, if this time is close to the time of the final PFS analysis, the contribution of components analysis will be conducted at the time of the final PFS analysis. As these treatment comparisons are secondary and serve a different purpose to that of the primary comparisons, they are not included in the multiple testing procedure for the primary comparisons, and an alpha of 0.05 will be used for either PFS or OS without multiplicity adjustment.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

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

Efficacy data will be summarised and analysed on the Full (ITT) analysis set.

PK data will be summarised and analysed on the PK analysis set.

Safety data will be summarised on the safety analysis set.

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

Table 29 details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

Table 29 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints Analysed	Notes
Overall Survival	Sub-study A PD-L1-positive population – hazard ratio comparing MEDI4736 versus Standard of Care Sub-study B PD-L1-negative population – stratified log rank test comparing MEDI4736+tremelimumab versus Standard of Care Sub-study B only Sensitivity analysis using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias Sub-study B The following secondary treatment comparisons will be performed dependent upon the results of the contribution of components analysis: i) MEDI4736+tremelimumab versus MEDI4736 ii) MEDI4736+tremelimumab versus tremelimumab iii) MEDI4736 versus Standard of Care iv) Tremelimumab versus Standard of Care Supportive analysis on Sub-study B only Subgroup analysis using Cox proportional hazards models Secondary analysis using Cox proportional hazards models to determine the effect of covariates on the HR estimate Secondary analysis using Cox proportional hazards models to determine the consistency of treatment effect between subgroups via the approach of Gail and Simon 1985.

Table 29 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints Analysed	Notes
Progression Free Survival	Co-primary analysis <u>Sub-study A</u> PD-L1-positive population – hazard ratio using site investigator data (RECIST 1.1) comparing MEDI4736 versus Standard of Care <u>Sub-study B</u> PD-L1-negative population – stratified log rank test using site investigator data (RECIST 1.1) comparing MEDI4736+tremelimumab versus Standard of Care Sensitivity analyses using site investigator data (RECIST 1.1) 1) Interval censored analysis – evaluation time bias 2) Analysis using alternative censoring rules – attrition bias <u>Sub-study B only</u> The following secondary treatment comparisons will be performed dependent upon the results of the contribution of components analysis: i) MEDI4736+tremelimumab versus MEDI4736 ii) MEDI4736+tremelimumab versus tremelimumab iii) MEDI4736 versus Standard of Care iv) Tremelimumab versus Standard of Care <u>Supportive analysis on Sub-study B only</u> Subgroup analysis using Cox proportional hazards models Secondary analysis using Cox proportional hazards models to determine the effect of covariates on the HR estimate Secondary analysis using Cox proportional hazards models to determine the consistency of treatment effect between subgroups via the approach of Gail and Simon 1985.
The analyses specified below will be performed in each of the Sub-studies A and B:	
Proportion of patients alive at 12 months	Hazard ratio using the Kaplan-Meier estimates of survival at 12 months (following the method described by Klein et al 2007)
Objective Response Rate	Logistic regression using site investigator data (RECIST 1.1); Sub-study B only
Proportion of patients alive and progression free at 6 and 12 months	Hazard ratio using the Kaplan Meier estimates of progression free survival at 6 and 12 months (following method described by Klein et al 2007)
Time from randomisation to second progression	Stratified log-rank test
Symptom improvement rate (EORTC QLQ-C30 and LC13 endpoints)	Logistic regression

Table 29 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints Analysed	Notes
QoL/Function improvement rate (EORTC QLQ-C30 endpoints)	Logistic regression
Time to QoL/Function deterioration (EORTC QLQ-C30 endpoints)	Stratified log-rank test in Sub-study B. Hazard ratios only in Sub-study A
Time to symptom deterioration (EORTC QLQ-C30 and LC13 endpoints)	Stratified log-rank test in Sub-study B. Hazard ratios only in Sub-study A
CCI [redacted]	[redacted]

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; LC13 Lung Cancer Module; PD-L1 Programmed death ligand 1; QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumours; Sub-study A MEDI4736 monotherapy v Standard of Care; Sub-study B MEDI4736+tremelimumab v Standard of Care.

All outputs will be summarised for each sub-study by treatment arm for all randomised patients (ITT).

12.2.1 Multiple testing strategy

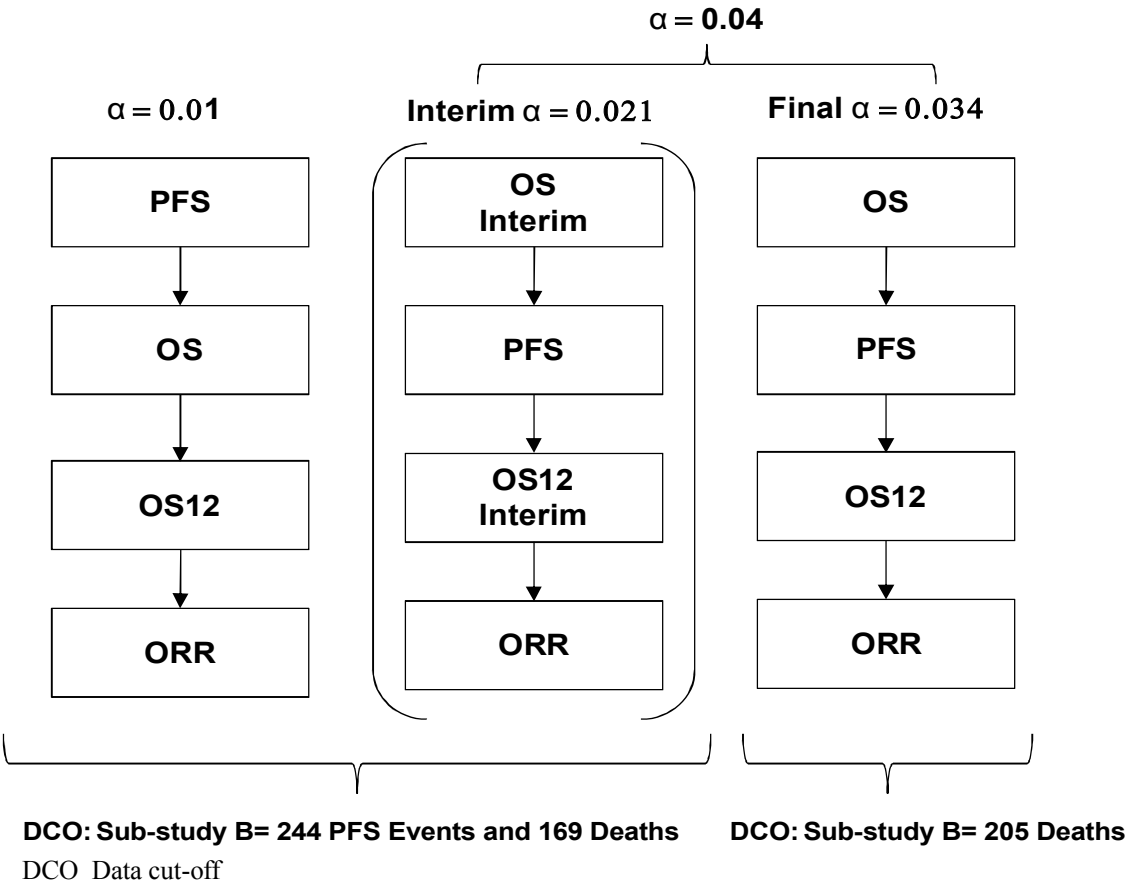
The multiple testing procedure will define which significance levels should be applied to the interpretation of the raw p-values for the 2 primary endpoints of PFS and OS and the key secondary endpoints of OS12 and ORR in Sub-study B.

The overall type I error of 0.05 will be split between the co-primary endpoints OS and PFS. To control for type I error, an alpha of 0.04 will be used for the analysis of OS and an alpha of 0.01 will be used for the analysis of PFS. The study will be considered positive if the PFS analysis results and/or the OS analysis results are statistically significant in Sub-study B. The 0.04 alpha level allocated to OS will be controlled at the interim and primary time point 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.

In Sub-study B, an interim OS analysis for superiority and the primary PFS analysis will occur at the same time and the primary OS analysis will be performed when 205 deaths have accumulated from patients who have been randomised to the MEDI4736+tremelimumab and Standard of Care arms. For example, if 82% of the deaths required at the time of the primary OS analysis are available at the time of the interim (ie, 169/205 deaths have occurred), the 2-sided alpha level to be applied in the OS interim analysis would be 0.021 and the 2-sided alpha level to be applied for the primary OS analysis would be 0.034.

At the time of the primary PFS, interim OS and primary OS analyses, the primary and key secondary hypotheses will be tested on the primary treatment comparisons only, for Sub-study B, using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). No adjustment will be made for the contribution of components analysis on Sub-study B as it is not concerned with testing the primary treatment comparison. With this approach, hypotheses will be tested in a pre-defined order. At the time of the primary PFS analysis, the PFS endpoint will be tested first and at the time of the primary OS analysis, the OS endpoint will be tested first. The other hypotheses corresponding to secondary endpoints will then be tested in a pre-specified hierarchy following PFS and OS rejection. 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 0.05 (2-sided), amongst all key hypotheses. Figure 6 shows the multiple testing framework for Sub–study B. Alpha will be recycled within Sub-study B.

Figure 6 **Multiple testing procedures for controlling the type 1 error rate for Sub-study B**



DCO Data cut-off

Upon achieving statistical significance on the PFS endpoint in Sub-study B, the testing of the OS endpoint will be performed hierarchically as illustrated in Figure 6. Similarly the testing of the PFS endpoint will be done subsequent to achieving statistical significance on the

interim/primary OS endpoint in Sub-study B. If both of these endpoints are significant, the alpha level can be combined and passed down to lower levels in the hierarchy. Spending alpha between endpoints in this way will strongly control type I error (Glimm et al 2010).

It is currently anticipated that the cut-off for PFS co-primary analysis will be before the cut-off for OS co-primary analysis. Alpha will be recycled across the PFS and OS hierarchies at the time of the final analysis of the respective endpoints. If the PFS and OS analyses are closely aligned and performed at the same time, the same alpha split (0.01vs. 0.04) will be applied to the PFS analysis and OS analysis, and the alpha will be recycled between PFS and OS if either of them is significant.

12.2.2 Co-primary endpoints

12.2.2.1 Overall survival

Overall survival will be analysed in Sub-study B using a stratified log-rank test adjusting for Standard of Care therapy type (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other). The effect of treatment will be estimated by the HR together with its corresponding ([1-adjusted alpha] x 100)% CI and p-value. Note that the alpha-adjusted CI and p-value will only be generated on Sub-study B. The HR and 95% CI will be generated on Sub-study A. The boundaries (ie, adjusted alpha levels) for the treatment comparison at the interim and final analysis for OS for Sub-study B 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 12.2.14). In Sub-study B, any of the secondary treatment comparisons at the time of final analysis will display the 95% CI.

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

Kaplan-Meier plots of OS will be presented by treatment arm within each sub-study. 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.

OS12 will be summarised (using the Kaplan-Meier curve) and presented by treatment arm. Each will be compared between treatments by using the Kaplan-Meier estimator of OS at 12 months for each treatment to obtain the HR. The HR and CI will be presented using the following approach (Klein et al 2007):

- The *HR(group1:group2)* is estimated as $\frac{\ln \hat{S}_1(t)}{\ln \hat{S}_2(t)}$
- The variance for *ln(HR)* is estimated as $\frac{\hat{\sigma}_1(t)^2}{\ln^2 S_1(t)} + \frac{\hat{\sigma}_2(t)^2}{\ln^2 S_2(t)}$

where $\hat{\sigma}_i(t)^2 = \sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}$ is the variance for *ln{S(t)* derived from greenwood's formula for the variance of *S(t)*and can be estimated from standard software packages, where d_i and n_i

refer to the number of deaths and patients at risk for each risk set. The *ln(HR)* and its variance in each strata will be estimated and combined by weighting inversely proportionately according to each within stratum variance (Whitehead and Whitehead 1991).

For Sub-study B, the assumption of proportionality will be assessed, initially only with regards to the primary treatment comparison. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be as a result of treatment-by-covariate interactions, which may be investigated.

A sensitivity analysis for OS (Sub-study B only) will examine the censoring patterns to rule out attrition bias with regards to the primary treatment comparisons, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

Subgroup analyses will be conducted in Sub-study B comparing OS between the treatments concerned in the primary treatment comparison in the following subgroups of the FAS:

- Sex (male versus female)
- Age at randomisation (<65 versus ≥65 years of age)
- Histology (squamous versus all other)
- Smoking (smoker versus non-smoker [never smoked])
- Standard of Care grouped (gemcitabine/vinorelbine versus erlotinib)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic factors.

No adjustment to the significance level for testing will be made since all these analyses will be considered supportive of the primary analysis of OS.

Cox proportional hazards modelling will be employed to assess the effect of covariates on the HR estimate for the primary treatment comparison for Sub-study B. A model will be constructed, containing treatment and the stratification factors, to ensure any output from the Cox modelling is likely to be consistent with the results of the stratified log-rank test.

Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985.

For each subgroup, the HR (MEDI4736+tremelimumab: Standard of Care in Sub-study B) and 95% CI will be calculated from an unstratified Cox proportional hazards model with treatment as the only covariate.

These HRs and associated 2-sided 95% CIs will be summarised and presented on a forest plot, along with the results of the overall primary analysis.

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 OS will not be formally analysed. In this case, only descriptive summaries will be provided.

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

CCI [redacted]

12.2.2.2 Progression free survival

Progression free survival based upon the site investigator data will be analysed in each sub-study using the same methodology as described for the OS analyses.

The effect of treatment will be estimated by the HR together with its corresponding 99% CI and p-value for Sub-study B. The HR and 95% CI will be generated on Sub-study A. In Sub-study B, if the contribution of components analysis was performed at an earlier time point than the final PFS analysis, for the treatment comparisons tested at both the interim and the final analyses, a corresponding ([1-adjusted alpha] x 100)% CI will be produced. Kaplan-Meier plots of PFS will be presented by treatment arm for each sub-study. 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.

The following sensitivity analyses will only be performed for the primary treatment comparison in Sub-study B.

The assumption of proportionality will be assessed in the same way as for OS. The analysis will be based on the PFS from the site investigator data.

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint

between the time of progression and the previous evaluable RECIST assessment will be analysed using a log-rank test. For patients whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2, or more, non-evaluable tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

Subgroup analyses and a forest plot will be generated comparing PFS between treatments in the same way as previously specified for OS.

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

12.2.3 Objective response rate

Objective response rate will be based on the site investigator assessments and will use all scans regardless of whether they were scheduled or not. The ORR will be compared between MEDI4736 versus Standard of Care in Sub-study A and MEDI4736+tremelimumab versus Standard of Care in Sub-study B using logistic regression models adjusting for the same factors as the co-primary endpoints. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% CI. A p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model) will only be generated in Sub-study B.

Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR). Overall visit response data will be listed and summarised over time for all patients (ie, the FAS). For each treatment arm, best objective response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD and NE). No formal statistical analyses are planned for BoR.

12.2.4 Duration of response

For both sub-studies, descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

12.2.5 Proportion of patients alive and progression free at 6 months

The proportion of patients alive and progression free at 6 months will be summarised (using the Kaplan-Meier curve) and presented by treatment arm. APF6 will be compared between treatments by using the Kaplan-Meier estimator of PFS at 6 months for each treatment to

obtain the HR. The HR and CI will be presented using the following approach (Klein et al 2007):

- The *HR(group1:group2)* is estimated as $\frac{\ln \hat{S}_1(t)}{\ln \hat{S}_2(t)}$
- The variance for *ln(HR)* is estimated as $\frac{\hat{\sigma}_1(t)^2}{\ln^2 S_1(t)} + \frac{\hat{\sigma}_2(t)^2}{\ln^2 S_2(t)}$

where $\hat{\sigma}_i(t)^2 = \sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}$ is the variance for ln{S(t) derived from greenwood's formula for the variance of *S(t)* and can be estimated from standard software packages, where d_i and n_i refer to the number of deaths and patients at risk for each risk set.

The *ln(HR)* and its variance in each strata will be estimated and combined by weighting inversely proportionately according to each within stratum variance (Whitehead and Whitehead 1991).

12.2.6 Proportion of patients alive and progression free at 12 months

The proportion of patients alive and progression free at 12 months will be summarised (using the Kaplan-Meier curve) and presented by treatment arm. Each will be compared between treatments by using the Kaplan-Meier estimator of PFS at 12 months for each treatment to obtain the HR. The HR and CI will be presented using the same approach as for APF6 (Section 12.2.5).

12.2.7 Time from randomisation to second progression

Time from randomisation to second progression will be analysed using identical methods as outlined for the analysis of PFS for Sub-study B only and adjusting for the same set of covariates, but no subgroup analysis will be performed. Medians and Kaplan–Meier plots will be presented to support the analysis.

For supportive purposes, the time to the start of subsequent therapy will be analysed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan-Meier plot of the time to the start of subsequent therapy will be presented by treatment arm and the time between progression and starting subsequent therapy will be assessed. No multiplicity adjustment will be applied as these are viewed as supportive endpoints.

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

12.2.8 Patient reported outcomes

The PRO endpoints that have been identified as primary are EORTC QLQ-C30 time to QoL deterioration for global health status and LC13 time to symptom deterioration for each of

dyspnea, cough, hemoptysis, and pain. These are not part of the main multiple testing procedure and as supportive endpoints will need a Bonferroni adjustment to the significance level to aid interpretation. Therefore, these 5 endpoints will be tested at a 1% significance level and 99% CIs will be produced.

The other time to symptom deterioration endpoints will be tested at a 5% significance level and 95% CIs will be produced.

12.2.8.1 EORTC QLQ-C30

Time to symptom deterioration will be analysed for each of the 3 symptom scales (fatigue, pain, nausea/vomiting) and the 5 individual symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea). Time to QoL/function deterioration will be analysed for the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL. This will be achieved by comparing between treatment arms using a stratified log-rank test as described for the primary analysis of OS. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

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. Symptom improvement rate and QoL/function improvement rate will be analysed by comparing between treatment arms using a logistic regression model as described for the analysis of ORR. The odds ratio and 95% CI for each scale/item will be presented graphically on a forest plot.

For each of the 3 symptom scales (fatigue, pain, nausea/vomiting), 5 individual symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea), 5 functional scales (physical, role, emotional, cognitive, and social), and global health status/QoL, time to deterioration will be presented using a Kaplan-Meier plot. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death, and the median time to deterioration will also be provided for each treatment arm.

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 arm. 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 11.3.1.1) will also be produced for each treatment arm.

12.2.8.2 LC13

Time to symptom deterioration for each of the 6 individual symptoms (dyspnoea, cough, haemoptysis, chest pain, arm/shoulder pain, other pain) will be compared between treatment arms using a stratified log-rank test as described for the primary analysis of OS. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

For each of the 6 symptoms items in LC13, time to deterioration in symptoms will be presented using a Kaplan-Meier plot. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death, and the median time to deterioration will also be provided for each treatment arm.

A summary of the symptom improvement rate for each of the 6 individual symptom items will be produced. The symptom improvement rate will be compared between treatment arms using a logistic regression model as described for ORR. The odds ratio and 95% CI for each symptom will be presented graphically on a forest plot.

Summaries of original and change from baseline values of each symptom (dyspnoea, cough, haemoptysis, 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 arm. 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 11.3.1.2) will also be produced for each treatment arm.

12.2.8.3 EuroQol 5-Dimension 5-Level questionnaire

CCI

[redacted]

12.2.9 Healthcare resource use

CCI

[redacted]

12.2.10 Safety data

Safety and tolerability data will be presented by treatment arm in each sub-study 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 summarised by treatment arm 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 monotherapy in Sub-study A or retreatment with MEDI4736+tremelimumab or MEDI4736 monotherapy or tremelimumab monotherapy in Sub-study B will be produced separately.

Other safety data will be assessed in terms of physical examination, clinical chemistry, haematology, vital signs and ECGs. Within each sub-study, exposure to MEDI4736 monotherapy (Sub-studies A and B), MEDI4736+tremelimumab (Sub-study B), tremelimumab monotherapy (Sub-study B) and Standard of Care will be summarised. Time on study, MEDI4736/tremelimumab/Standard of Care dose delays/interruptions and dose reductions in the Standard of Care arm will also be summarised. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

12.2.11 PK data (MEDI4736 monotherapy, MEDI4736+tremelimumab and tremelimumab monotherapy arms only)

Pharmacokinetic concentration data will be listed for each patient and each dosing day, and a summary provided for all evaluable patients in each sub-study.

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/or anti-tremelimumab antibodies. The immunogenicity titre and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-MEDI4736 antibodies and/or anti-tremelimumab antibodies.

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

12.2.12 PK/PDx relationships (MEDI4736 monotherapy, MEDI4736+tremelimumab and tremelimumab monotherapy arms only)

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modelling approach.

12.2.13 Biomarker data

CCI [redacted]

CCI

[redacted]

12.2.14 Interim analysis

An interim analysis will be performed to test OS on the primary treatment comparison on Sub-study B. It will be performed at the time of the final PFS analysis when approximately 244 PFS events have occurred in patients who have been randomised to the MEDI4736+tremelimumab and Standard of Care arms. However, for practical considerations, if it happens that the analysis time points for the final PFS and OS analyses are closely aligned, based on the occurrences of the events, then one single analysis of OS will be conducted along with the PFS analysis In this case, the entire 0.04 alpha will be utilized for this OS analysis.

All interim analyses will be assessed by an IDMC (further details are given in the IDMC charter). It is probable that recruitment will have completed prior to the results of the interim analysis being available.

Overall survival

No interim analysis will be performed on Sub-study A.

For Sub-study B, the criterion for superiority is a statistically significant improvement in OS at the interim analysis. The Lan and DeMets approach that approximates the O'Brien Fleming spending function will be used to account for multiplicity introduced into the treatment comparison by including the interim analysis for superiority (Lan and DeMets 1983).

It is expected that approximately 169 (82% of the target 205) deaths will be observed in the study. If 82% of the deaths required (assuming a HR of 0.63) at the time of the primary OS analysis (approximately 56% maturity) are available at the time of the interim (ie, 169/205 deaths have occurred), the 2-sided alpha level to be applied in the OS interim analysis would be 0.021. This analysis would have 69% power to detect a HR of 0.65. The minimal difference in OS that would be deemed statistically significant is an average HR of 0.70.

It is estimated that this interim analysis will be performed approximately 18 months after the start of randomisation.

Under the above assumptions the 2-sided alpha level to be applied for the primary OS analysis would be 0.034.

If the PFS and/or OS results indicate superiority, then analyses of all other endpoints would be performed and the results of these analyses will form the basis for submissions for regulatory

approval. Patients would continue to be followed for survival until the required number of patients have died, when an updated analysis would be performed.

If the PFS result is not statistically significant and the OS interim analysis result does not meet the criterion of stopping for superiority, then the extended study team at AstraZeneca/MedImmune will remain blinded and the patients will continue to be followed for survival.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypotheses as described in Section 1.2.

The co-primary endpoints in Sub-study B are OS and PFS. To control for type I error, an overall alpha level of 0.04 will be used for analysis of OS (accounting for 1 formal interim analysis to assess efficacy) and an overall alpha level of 0.01 will be used for analysis of PFS. Sub-study B will be considered positive (a success) if either the PFS analysis results and/or the OS analysis results are statistically significant.

A total of approximately 1300 patients are expected to be recruited in the study to achieve approximately 610 evaluable patients in the study (approximately 126 patients in Sub-study A and 480 patients in Sub-study B). The PD-L1-positive population is assumed to be approximately 30% of total population (AstraZeneca, unpublished data). If the prevalence assumption does not hold then it is likely that recruitment will need to be extended. The sample sizing for each sub-study assumes a delay in separation of the survival curves between each arm hence the use of average HRs.

OS analysis

The OS analysis in Sub-study A (PD-L1-positive population) will be performed when approximately 82 deaths have occurred from 126 patients (65% maturity).

The OS analysis in Sub-study B (PD-L1-negative population) will be performed when 205 deaths have occurred from the 300 patients (68% maturity) who have been randomised to the MEDI4736+tremelimumab and Standard of Care arms. Assuming the true average HR is 0.63 in PD-L1-negative population for OS (corresponding to a 4.4-month improvement in median OS from a control group median of 7 months), this analysis will have 90% power to demonstrate a statistically significant difference for OS, assuming an overall alpha level of 0.04 2-sided. The minimal difference in OS that could be deemed statistically significant in Sub-study B is an average HR of 0.75. A 15-month recruitment period and a minimum follow-up period of 12 months is assumed on Sub-study B for OS. Therefore it is anticipated that this OS analysis could be performed 27 months after the first patient has been recruited. Assuming that the survival curves of the two treatment arms do not separate for 2 months then the HR after that point would need to be 0.53 to produce an average HR of 0.63 over the follow-up period. This would be associated with 12-month survival rates of 30.5% for Standard of Care and 48.5% for MEDI4736+tremelimumab.

PFS analysis

The PFS analysis in Sub-study A (PD-L1-positive population) will be performed at the same time as the OS analysis on Sub-study A.

The PFS analysis in Sub-study B (PD-L1-negative population) will be performed when approximately 244 PFS events have occurred from 300 patients (81% maturity) who have been randomised to the MEDI4736+tremelimumab and Standard of Care arms. Assuming the true average HR is 0.63 in PD-L1-negative population for PFS (corresponding to a 1.3-month improvement in median PFS from a control group median of 3 months), this analysis will have 84% power to demonstrate a statistically significant difference for PFS, assuming an alpha level of 0.01 2-sided. The minimal difference in PFS that would be deemed statistically significant in Sub-study B is an average HR of 0.72. Sub-study B is expected to have a recruitment period of 15 months and a follow-up period of 7 months for the PFS endpoint. Therefore it is anticipated that this PFS analysis could be performed at a minimum of 22 months after the first patient has been recruited. If the survival curves of the 2 treatment arms do not separate for 2 months then the HR after that point would need to be 0.43 to produce an average HR of 0.63 over the follow-up period. This would be associated with 12-month PFS rates of 6.3% for Standard of Care and 23.3% for MEDI4736+tremelimumab.

Please refer to Appendix D for information on PGx.

12.4 Independent data monitoring committee

This study will use an external IDMC to assess ongoing safety analyses on both sub-studies as well as the interim analyses for superiority. The committee will meet approximately 6 months after the study has started or 20 patients have been randomised to the combination arm (whichever comes first) to review the safety data from the study. The IDMC will meet approximately every 6 months thereafter. Following each meeting, the IDMC will report to the sponsor and may recommend changes in the conduct of the study.

This committee will be composed of therapeutic area experts and biostatisticians, who are not employed by AstraZeneca/MedImmune and do not have any major conflict of interest.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca/MedImmune. The report will include the recommendation and any potential protocol amendments, and will not contain any unblinding information.

The final decision to modify or stop the study will sit with the sponsor. The sponsor or IDMC may call additional meetings if at any time there is concern about the safety of the study.

In addition:

- If the contribution of components analysis is performed prior to the final PFS analysis, the IDMC will review the efficacy data on Sub-study B for the MEDI4736+tremelimumab versus tremelimumab monotherapy treatment comparison and the MEDI4736+tremelimumab versus MEDI4736 monotherapy treatment comparison.

- The IDMC will review the efficacy data on Sub-study B at the time of the final PFS analysis when approximately 244 PFS events have occurred from patients randomised to the MEDI4736+tremelimumab and Standard of Care arms, at approximately 22 months post first randomisation, at the time of the primary analysis of PFS and interim analysis of OS.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

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

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies, AstraZeneca/MedImmune and QuintilesIMS contacts

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, see Section 6.4.4.**

In the case of a medical emergency the investigator may contact the 24-hour QuintilesIMS Medical Emergency Contact Centre PPD or alternative number PPD. After final DCO, the investigator should contact AstraZeneca/MedImmune Patient Safety using the contact information specified below:

Name	Role in the study	Address & telephone number
PPD	Study Delivery Team Leader	QuintilesIMS Ltd 500 Brook Drive Green Park Reading United Kingdom Office: PPD
PPD	Senior Director Physician	Mereside Alderley Park, Macclesfield Cheshire, SK10 4TG Tel: PPD
Patient Safety	AstraZeneca/MedImmune Patient Safety	BUDAPEST: c/o PPD Tata Consultancy Services Office Garden 2, 3rd floor Aliz utca 2 Budapest - 1117, Hungary MUMBAI: c/o PPD Tata Consultancy Services 4th Floor, Tiffany, Hiranandani Business Estate Thane - West, 400607 AEMailbox: PPD

13.2 Overdose

Use of MEDI4736, tremelimumab or MEDI4736+tremelimumab 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 MEDI4736 or tremelimumab and possible symptoms of overdose are not established.

Please also refer to the local prescribing information for the relevant Standard of Care agent (eg, gemcitabine prescribing information, NAVELBINE® prescribing information, TARCEVA® prescribing information).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose case report form module.

- An overdose without associated symptoms is only reported on the Overdose case report form module.

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

The designated AstraZeneca/MedImmune representative (ie, QuintilesIMS) works with the investigator to ensure that all relevant information is provided to the AstraZeneca/MedImmune Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

If an overdose on an AstraZeneca study drug occurs after the final DCO, then investigators or other site personnel shall inform **AstraZeneca/MedImmune Patient Safety** immediately, or **no later than 24 hours** of when he or she becomes aware of it.

13.3 Pregnancy

All outcomes of pregnancy should be reported to the AstraZeneca/MedImmune representative (ie, QuintilesIMS). Following the final DCO, investigators or other site personnel shall report all pregnancy outcomes to **AstraZeneca/MedImmune Patient Safety.**

13.3.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of 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, investigators or other site personnel must inform appropriate AstraZeneca/MedImmune representatives (ie, QuintilesIMS) immediately, or **no later than 24 hours** from when he or she becomes aware of it.

If any pregnancy occurs after the final DCO, investigators or other site personnel must inform **AstraZeneca/MedImmune Patient Safety** immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca/MedImmune representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca/MedImmune Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy. Paper-based modules will be available to sites following the final DCO.

13.3.2 Paternal exposure

Information on the pregnancy of a patient's partner must be obtained directly from the patient's partner. Therefore, prior to obtaining information on the pregnancy, the investigator must obtain the consent of the patient's partner.

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days (if in the MEDI4736 monotherapy arm) or 180 days (if in the tremelimumab or MEDI4736+tremelimumab arm) following the last dose of study drug. Please follow the local prescribing information relating to contraception and the time limit for such precautions for agents in the Standard of Care arm (eg, gemcitabine prescribing information, NAVELBINE® prescribing information, TARCEVA® prescribing information).

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

The outcome of any conception occurring from the date of the first dose until 90 days (180 days if on tremelimumab or MEDI4736+tremelimumab treatment) after the last dose of study treatment (MEDI4736, tremelimumab, MEDI4736+tremelimumab or Standard of Care) should be followed up and documented.

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