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| **Revised Clinical Study Protocol 06** | |
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# A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

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**EudraCT number: 2014-000336-42**

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**The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:**

| Amendment No. | Date of Amendment | Local Amendment No: | Date of Local Amendment |
|---|---|---|---|
| 01 | 10 June 2014 | | |
| 02 | 08 August 2014 | | |
| 03 | 18 February 2015 | | |
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| 07 | 05 June 2019 | | |
| 07.1 | 04 September 2019 | | |

| Administrative Change No. | Date of Administrative Change | Local Administrative Change No. | Date of Local Administrative Change |
|---|---|---|---|
| 01 | 30 October 2014 | | |

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# PROTOCOL SYNOPSIS

## A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

### International Co-ordinating Investigator

PPD
Durham, NC 27707, United States.

### Study centre(s) and number of patients planned

Approximately 1000 patients with locally advanced, unresectable non-small cell lung cancer (NSCLC; Stage III) will be recruited and 702 patients randomised at 260 to 330 sites in Australia, Asia, Europe, North and South America and South Africa. These patients will be in complete response (CR), partial response (PR), or have stable disease (SD) following definitive, platinum-based, concurrent chemoradiation therapy.

| Study period | | Phase of development |
|---|---|---|
| Estimated date of first patient enrolled | Q2 2014 | 3 |
| Estimated date of last patient completed | Q2 2021 | 3 |

### Objectives

| Primary Objective: | Outcome Measure: |
|---|---|
| To assess the efficacy of MEDI4736 treatment compared with placebo in terms of OS and PFS | OS<br>PFS using BICR assessments according to RECIST 1.1[a] |

a The co-primary analysis of PFS will be based on programmatically derived PFS BICR assessment according to RECIST 1.1. See the statistical methods section for further details.
BICR Blinded Independent Central Review; OS Overall survival; PFS Progression free survival; RECIST Response Evaluation Criteria In Solid Tumours.

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| To further assess the efficacy of MEDI4736 compared with placebo in terms of: OS24, ORR, DoR, APF12, APF18, PFS2, and TTDM | OS24<br>ORR using BICR assessments according to RECIST 1.1a<br>DoR using BICR assessments according to RECIST 1.1a<br>APF12 and APF18 using BICR assessments according to RECIST 1.1<br>PFS2 as defined by local standard clinical practice<br>TTDM using BICR assessments according to RECIST 1.1a |
| To assess the safety and tolerability profile of MEDI4736 compared with placebo | AEs, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, haematology and urinalysis |
| To assess the PK of MEDI4736 | Concentration of MEDI4736 in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling) |
| To investigate the immunogenicity of MEDI4736 | ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed]) |
| To assess symptoms and health-related quality of life in patients treated with MEDI4736 compared with placebo 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)<br>LC13: Time to symptom deterioration (dyspnoea, cough, haemoptysis, chest pain, arm/shoulder pain, other pain)<br>Changes in World Health Organization Performance Status will also be assessed |

Analysis of ORR and DoR will be based upon BICR assessment according to RECIST 1.1. See the statistical methods section for further details.

Note: Prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

ADA Anti-drug antibody; AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomisation; APF18 Proportion of patients alive and progression free at 18 months from randomisation; BICR Blinded Independent Central Review; 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; OS24 Proportion of patients alive at 24 months from randomisation; PFS2 Time from randomisation to second progression; PK Pharmacokinetic(s); QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumours; TTDM Time to death or distant metastasis.

| **Exploratory Objective:** | **Outcome Measure:** |
|---|---|
| To explore irRC criteria as an assessment methodology for clinical benefit of MEDI4736 compared with placebo by BICR | PFS and ORR using BICR assessments according to irRC |
| To investigate the relationship between MEDI4736 PK exposure and clinical outcomes, efficacy, AEs and/or safety parameters, if deemed appropriate | A graphical and/or a data modelling approach will be used to analyse MEDI4736 PK exposure and the relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate |
| To describe and evaluate resource use associated with MEDI4736 treatment and underlying disease | Health resource utilisation measures including hospitalization, outpatient visits, or emergency department visits |
| To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L | The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data |
| To investigate the relationship between a patient's PD-L1 expression and spatial distribution within the tumour microenvironment and efficacy outcomes with MEDI4736 | Tumoural expression of PD-L1 and spatial distribution within the tumour microenvironment relative to efficacy outcomes (OS, PFS and ORR) |
| To collect blood and tissue samples for analysis of peripheral and tumoural biomarkers | Biomarker analysis of blood and tissue to assess exploratory markers which may include but is not limited to: immune cell gene expression profiles within the peripheral and tumoural compartments, the presence of IFN-γ tumour necrosis factor-α, IL-2, IL-6, IL-10, IL-8, and IL-12 as well as antibodies against tumour, self, or viral antigens, expression of PD-L1 and the number and phenotype of immune cells such as T-cells |
| To explore the relationship(s) between a patient's biomarker status and MEDI4736 PK exposure and clinical outcomes before and after treatment | Biomarker status before and after treatment and MEDI4736 PK exposure and relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate |
| To explore potential biomarkers in residual biological samples (eg, tumour, plasma and/or serum), which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to MEDI4736 treatment | Correlation of biomarkers with response to MEDI4736 treatment and/or the progression of cancer |
| To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study drugs and/or susceptibility to disease (optional) | Correlation of polymorphisms with variation in PK, PDx, safety or response parameters observed in patients treated with MEDI4736 and/or susceptibility to disease |

AE Adverse event; BICR Blinded Independent Central Review; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; IFN Interferon; IL Interleukin; irRC Immune-related response criteria; ORR Objective response rate; OS Overall survival; PD-L1 Programmed death ligand 1; PDx Pharmacodynamic(s); PFS Progression free survival; PK Pharmacokinetic(s); T-cell T lymphocyte.

## Study design

This is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study assessing the efficacy and safety of MEDI4736 (also referred to as durvalumab) compared with placebo, as sequential therapy in male and female patients with locally advanced, unresectable NSCLC (Stage III), who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

Approximately 1000 patients will be enrolled and 702 patients randomised (patients will be in CR, PR or have SD following definitive, platinum-based, concurrent chemoradiation therapy) at 260 to 330 sites worldwide, in a 2:1 ratio (MEDI4736 to placebo) to 1 of 2 arms:

- MEDI4736 (10 mg/kg every 2 weeks [Q2W] intravenous [iv] for up to 12 months)
- Placebo (matching placebo for infusion Q2W iv for up to 12 months).

Randomisation will be stratified by: age at randomisation (<65 versus ≥65 years of age), sex (male versus female), and smoking history (smoker versus non-smoker). Patients must complete their last dose of radiation therapy within 1 to 42 days prior to randomisation in the study (the last dose of radiation therapy is defined as the day of the last radiation treatment session). For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy. For those patients randomised to the placebo arm no cross-in to the MEDI4736 arm is permitted and similarly those patients randomised to the MEDI4736 arm no cross-in to the placebo arm is permitted.

The primary objective of this study is to assess the efficacy of MEDI4736 treatment compared with placebo in terms of overall survival (OS) and progression free survival (PFS) per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR).

Tumour assessments will be performed using computed tomography/magnetic resonance imaging. The baseline assessment is part of the screening procedures and should be performed within 0 to 42 days after the end of chemoradiation therapy and before the start of study drug. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks (relative to the date of randomisation) for the first 12 months, then every 12 weeks thereafter, until confirmed objective disease progression as defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (irrespective of the reason for stopping study drug 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. A BICR will be conducted.

Following completion or discontinuation of study drug, 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.

There will be 4 DCO time points in the study. The first analysis DCO will occur when it is expected that 367 PFS events have occurred (52% maturity, approximately 30 months after the first patient is randomised). The second analysis DCO will occur at the time of the primary PFS analysis when it is expected that 458 PFS events have occurred (65% maturity, approximately 36 months after the first patient is randomised), and the first OS interim analysis will be conducted at the same time (with approximately 285 events, 41% maturity). The third analysis DCO will occur at the time of the second OS interim analysis when it is expected that 393 OS events have occurred (56% maturity, approximately 47 months after the first patient is randomised). The fourth analysis DCO will occur at the time of the primary OS analysis when it is expected that 491 OS events have occurred (70% maturity, at approximately 62 months). If the study achieves statistical significance for the co-primary endpoints of PFS and/or OS at one of the planned interim analyses, then that will be considered the final analysis for that endpoint. Further analyses for that particular endpoint may occur based on the needs for long term follow-up with more mature data.
See the Statistical methods section (Section 12.2) for further details.

At the time of Amendment 07 finalisation, the study endpoints had been met and the planned analysis portion of the study had been concluded. Details on long-term follow up, including data collection for patients in follow-up or in re-treatment, are provided in the Long-term follow up section (Section 9.5).

**Safety review and Independent Data Monitoring Committee (IDMC)**

An IDMC will be convened, and will meet approximately 3 months after the study has started, or once 75 patients have been randomised whichever occurs first, to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. The first three efficacy analyses will also be assessed by the IDMC. The committee will then meet again 3 months later and then at least every 6 months thereafter up to the decision to unblind the study. Serious adverse events, adverse events, and other safety data will be reviewed and individual and aggregated safety data will be evaluated by the IDMC. In addition the IDMC will review the unblinded interim analysis summaries of efficacy data. 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- or cytologically-documented NSCLC who present with locally advanced, unresectable (Stage III) disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology). Patients must not have progressed following definitive, platinum-based, concurrent chemoradiation therapy; the last session of radiation therapy must be completed within 1 to 42 days prior to randomisation in the study. For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy. Patients must have World Health Organization Performance Status of 0 or 1.

**Investigational product, dosage and mode of administration**

Patients enrolled to the MEDI4736 arm will receive MEDI4736 10 mg/kg via a 60-minute iv infusion Q2W ± 3 days for up to 12 months (maximum of 26 doses, last dose at Week 50).

**Comparator, dosage and mode of administration**

Patients enrolled to the placebo arm will receive matching placebo via a 60-minute iv infusion Q2W ± 3 days for up to 12 months (maximum of 26 doses, last dose at Week 50).

**Duration of treatment**

Patients enrolled in the study will receive either MEDI4736 10 mg/kg or placebo via iv infusion Q2W ± 3 days. Administration of study drug (ie, investigational product MEDI4736 or placebo) will commence on Day 1 following randomisation to MEDI4736 or placebo after confirmation of eligibility and will continue on a Q2W schedule for a maximum duration of 12 months. The final administration of study drug will be at the Week 50 visit. Study drug 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 study drug), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue study drug occur.

Disease progression requires confirmation. The confirmation scan should be acquired at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior determination of tumour progression. In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study drug until progression has been confirmed.

If progression is not confirmed, then the patient should continue study drug and on treatment assessments.

Patients who achieve and maintain disease control (CR, PR, no evidence of disease or SD) through to the end of the 12-month treatment period will enter follow-up. Upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up after completion of 12 months of treatment, patients initially treated with MEDI4736 may restart and continue on study drug for as long as the Investigator judges that they are gaining clinical benefit with the same treatment guidelines followed during the initial 12-month treatment period. If the patient continues to receive re-treatment after the final DCO for the study, they should have tumour assessment scans and other assessments as per local clinical practice. Patients will only be able to restart study drug once. Once the study has been unblinded, then only patients who were randomised to the durvalumab (MEDI4736) treatment arm and who fulfil the eligibility criteria for re-treatment will be able to restart study drug.

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 re-restarting study drug, and cannot continue to receive study drug, will enter follow-up.

Patients with confirmed PD that 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 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.

Study drug should be discontinued if there is confirmed progression of disease (PD) following a previous response (PR or CR) to study drug.

For all patients who receive study drug through disease progression or patients who achieve disease control and restart study drug 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 re-treatment as specified in the protocol and also reconsent to continue or restart treatment. 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 study drug. Patients who progress during the first 12 months of treatment are not eligible for re-treatment at any time.

**Outcome variable(s):**

See Objectives.

**Statistical methods**

The primary objective of this study is to assess the efficacy of MEDI4736 treatment compared with placebo in terms of OS and PFS. OS is defined as the time from the date of randomisation until death due to any cause. PFS (per RECIST 1.1 as assessed by BICR) 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 two co-primary endpoints of this study are OS and PFS. To control for type-I error, a significance level of 2.5% will be used for analysis of OS and a significance level of 2.5% will be used for 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.

Secondary efficacy variables include: the proportion of patients alive at 24 months from randomisation, objective response rate, duration of response, the proportion of patients alive and progression free at 12 and 18 months from randomisation, the time from randomisation to second progression, time to relapse and time to death or distant metastasis.

Efficacy data will be summarised and analysed on an Intent-to-Treat (ITT) basis including all treated patients 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 drug are included in the ITT population.

Approximately 702 patients will be randomised 2:1 to MEDI4736 or placebo. There will be 4 DCO time points in the study. The DCO for the interim PFS analysis (first analysis) will be done when 367 PFS events have occurred (52% maturity). The interim PFS analysis will be assessed by an IDMC (further details are given in the IDMC charter). It is expected that recruitment will have completed prior to the results of the interim PFS analysis being available.

The DCO for the primary PFS analysis (second analysis) and first interim OS analysis will be done when at least 458 PFS events have occurred (65% maturity). If the true PFS hazard ratio (HR) is 0.67, this number of events in the study will provide at least 95% power to demonstrate a statistically significant difference for PFS with a 2-sided significance level of 2.5% in the ITT population; this translates to a 5-month benefit in median PFS over 10 months on placebo if PFS is exponentially distributed. The smallest treatment difference that would be statistically significant is a HR of 0.8. In addition, the first OS interim analysis will be performed for superiority, at the time of the primary PFS analysis. Approximately 285 death events (41% maturity) will be available for the first interim OS analysis (assuming OS HR=0.73). This interim OS analysis will also be assessed by an IDMC.

The DCO for the second OS interim analysis (third analysis) will occur when it is expected that 393 OS events have occurred (56% maturity).

The DCO for the primary OS analysis (fourth analysis) will occur when 491 OS events have occurred (70% maturity). If the true OS HR is 0.73, this number of death events will provide at least 85% power to demonstrate a statistically significant difference for OS, assuming a 2.5% 2-sided significance level in the ITT population; this translates to an 8-month benefit in median OS over 22 months on placebo if OS is exponentially distributed. The smallest treatment difference that would be statistically significant is a HR of 0.81.

OS will be analysed using a stratified log-rank test (age at randomisation [<65 years versus ≥65 years of age], sex [male versus female], and smoking status [smoker versus non-smoker]). The effect of treatment will be estimated by the HR together with its corresponding 97.5% confidence interval (CI) and p-value for the ITT population.

PFS, based on the programmatically derived PFS from BICR assessments, will be analysed using a stratified log-rank test. The effect of treatment will be estimated by the HR together with its corresponding 97.5% CI and p-value for the ITT population.

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

*End of Analysis Portion of Study*

Once the planned statistical analyses have been performed for both the primary analysis of PFS and OS endpoints of the study, data collection will be reduced. Please refer to Section 9.5.1 for more information.

Once the final DCO of the study for long term follow-up has been reached, patients in OS and PFS follow-up will be considered to have completed the study. At the time of the final DCO (anticipated to be approximately 5 years following the last patient randomised) any patient who is still in progression-free follow up will have been progression free for approximately 5 years following the start of their chemoradiation; as such, they will be considered cured and will no longer be considered eligible for re-treatment within this protocol. Those patients who are still actively in retreatment, and continuing to receive clinical benefit, will have the option to continue on study drug on an alternate rollover or extension protocol. Please refer to Section 9.5.2 for more information.

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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 |
|---|---|
| aa | Amino acid |
| ADA | Anti-drug antibody |
| AE | Adverse event (see definition in Section 6.4.1) |
| AESI | Adverse events of special interest |
| ALT | Alanine aminotransferase |
| APC | Antigen presenting cell |
| APF12 | Proportion of patients alive and progression free at 12 months from randomisation |
| APF18 | Proportion of patients alive and progression free at 18 months from randomisation |
| APTT | Activated partial thromboplastin time |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| B-cell | B lymphocyte |
| BICR | Blinded Independent Central Review |
| BoR | Best objective response |
| BP | Blood pressure |
| B7-H1 | B7 homolog 1 |
| cCTRT | Concurrent chemoradiation |
| CD | Cluster of differentiation |
| CI | Confidence interval |
| CL | Clearance |
| CR | Complete response |
| CRF | Case report form |
| 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 |

| Abbreviation or special term | Explanation |
|---|---|
| Cyno | Cynomolgus monkey |
| DCO | Data cut-off |
| DLT | Dose limiting toxicity |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of response |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDoR | Expected Duration of Response |
| EGFR | Epidermal growth factor receptor |
| EOI | End of infusion |
| 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 for Medical Oncology |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FFPE | Formalin fixed paraffin embedded |
| FTIH | First-Time-In-Human |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| hCG | Human chorionic gonadotropin |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| HRQoL | Health Related Quality of Life |
| IASLC | International Association for the Study of Lung Cancer |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation |
| IFN | Interferon |
| Ig | Immunoglobulin |
| IL | Interleukin |

| Abbreviation or special term | Explanation |
|---|---|
| imAE | immune-mediated adverse event |
| 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 |
| irRC | Immune-related response criteria |
| irRECIST 1.1 | Immune-related response criteria modified |
| ITT | Intent-to-Treat |
| 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 |
| MRI | Magnetic resonance imaging |
| mRNA | Messenger RNA |
| MTD | Maximum tolerated dose |
| NCCN | National Comprehensive Cancer Network |
| NE | Not evaluable |
| NED | No evidence of disease |
| 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 |
| OS24 | Proportion of patients alive at 24 months from randomisation |
| PD | Progression of disease |
| PD-1 | Programmed death 1 |
| PD-L1 | Programmed death ligand 1 |
| PDx | Pharmacodynamic(s) |

| Abbreviation or special term | Explanation |
|---|---|
| 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) |
| Q2W | Every 2 weeks |
| QoL | Quality of Life |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| r | Recombinant |
| 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) |
| $t_{½}$ | Half-life |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| T-cell | T lymphocyte |
| TMGs | Toxicity Management Guidelines |
| TSH | Thyroid stimulating hormone |
| TTDM | Time to death or distant metastasis |
| ULN | Upper limit of normal |
| US | United States |
| WBDC | Web Based Data Capture |
| WHO | World Health Organization |

# 1. INTRODUCTION

Investigators should be familiar with the MEDI4736 Investigator's Brochure (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 and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status and unresectable Stage III NSCLC is platinum-based doublet chemotherapy and radiotherapy administered with curative intent. A meta-analysis of concurrent versus sequential chemoradiotherapy showed better outcomes with concurrent therapy, but even with concurrent chemoradiotherapy 5-year overall survival (OS) is only approximately 15% (Butts et al 2014).

Therefore, sequential/maintenance (consolidation) therapy has been and continues to be explored in an attempt to prolong a favourable clinical state after delivery of definitive chemoradiotherapy.

### 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 (APCs) 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 APCs 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 APCs 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 lymphocytes, 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).

Blocking PD-L1 is a similar approach to that taken by ipilimumab, but has some potential advantages. Firstly, the expression of CTLA-4 and its ligands is restricted to the haematopoietic system; thus, the site of action for molecules targeting CTLA-4 is solely the peripheral lymphoid organs. In contrast, PD-L1 is expressed not only on cells of the haematopoietic system but also on a range of tumour types. Targeting of PD-L1 could therefore have additional effects within the tumour microenvironment. Secondly, CTLA-4 plays an early and critical role in controlling T-cell activation. This is reflected in the phenotype of CTLA-4 knockout mice, which die at an age of between 3 weeks and 4 weeks due to lymphoproliferative disease and tissue destruction. In contrast PD-L1, via binding to PD-1, acts later in the process of T-cell activation (Fife and Bluestone 2008) and is considered more dispensable for the control of initial T-cell activation. This is reflected in the phenotype of PD-L1 knockout mice, which are viable and have normal T-cell numbers and activation levels, but that have increased T-cell activation in response to antigen and increased susceptibility in certain autoimmunity models (Dong et al 2004, Latchman et al 2004). Based on these data, inhibition of PD-L1 would be expected to have reduced toxicity relative to inhibition of CTLA-4. In support of this, recent Phase I clinical studies testing the tolerability of agents targeting PD-1 have shown a more favourable toxicity profile than ipilimumab (Berger et al 2008, Brahmer et al 2010, Wolchok et al 2009).

#### 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 recently 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-related 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, 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 OS was 51 weeks (unpublished data presented by E Garon at The World Conference on Lung Cancer 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 recently 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 monoclonal antibody), 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.

### 1.1.3 MEDI4736

MEDI4736 is a human monoclonal antibody of the immunoglobulin (Ig) G1 kappa subclass that inhibits binding of PD-L1 (B7-H1, CD274) to PD-1 (CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the Ig G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma receptors involved in triggering effector function.

### 1.1.4 Non-clinical experience with MEDI4736

For full details of the non-clinical information, please refer to the current IB.

MEDI4736 binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. In vitro studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T-cells, resulting in restored proliferation and release of interferon (IFN) gamma. Additionally, MEDI4736 demonstrates a lack of antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity in cell-based functional assays. In vivo studies show that MEDI4736 inhibits tumour growth in a xenograft model via a T-cell dependent mechanism. An anti-mouse PD-L1 antibody has also demonstrated improved survival in a syngeneic tumour model when MEDI4736 was given as a monotherapy and resulted in complete tumour regression in >50% of treated mice when given in combination with chemotherapy.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics (PDx) and potential toxicity of MEDI4736. This conclusion was based on:

- The high amino acid (aa) sequence identity shared by the extracellular domains of cynomolgus monkey (cyno) PD-L1 and human PD-L1
- The conservation of an aa in cynoPD-L1 that is essential for the binding of MEDI4736 to recombinant (r)PD-L1
- The similar affinity for binding of MEDI4736 to rcynoPD-L1 and rPD-L1.

In addition, the PDx of MEDI4736 was demonstrated in vivo in cynomolgus monkeys.

Mouse and rat were not considered relevant nonclinical species due to:

- The much lower aa sequence identity shared by the extracellular domains of mouse PD-L1 or rat PD-L1 and human PD-L1
- Rat PD-L1 and mouse PD-L1 lack the aa that is essential for the binding of MEDI4736 to human PD-L1
- Lack of binding of MEDI4736 to the extracellular domains of mouse PD-L1.

Following intravenous (iv) administration, the PK of MEDI4736 in cynomolgus monkeys was non-linear. Systemic clearance (CL) decreased and half-life ($t_{½}$) increased with increasing doses, suggesting saturable target binding-mediated CL of MEDI4736. No apparent gender differences in PK profiles were observed for MEDI4736.

In general, there were no MEDI4736-related adverse effects in toxicology studies conducted in cynomolgus monkeys that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/PDx and dose range-finding study (4 doses over 5 weeks), and a GLP 4-week repeat-dose toxicity study were consistent with anti-drug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/PDx, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction based on the presence of ADA within days of the first dose, acuteness and timing (after repeated dosing) of the death, clinical signs consistent with an anaphylactic reaction, lack of remarkable effects on other study parameters, and lack of histopathologic findings consistent with any other cause of death. In addition, the spectrum of findings, especially the microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA-associated immune complex deposition. Similar effects have been observed by MedImmune in cynomolgus monkeys administered human monoclonal antibodies unrelated to MEDI4736: ADA immune-complexes were identified in the affected animal in a subsequent investigative study. Given that immunogenicity of human monoclonal antibodies in nonclinical species is not generally predictive of responses in humans, the ADA-associated morbidity and mortality were not taken into consideration for the determination of the no-observed-adverse-effect level of MEDI4736 in these studies. Finally, interim audited data from the dosing phase of the pivotal 3-month GLP toxicity study in cynomolgus monkeys, showed that subchronic dosing of MEDI4736 was not associated with any adverse effects. Therefore, the no-observed adverse effect level of MEDI4736 in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies.

### 1.1.5 Clinical experience with MEDI4736

For full details of the clinical information, please refer to the current IB.

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 are based on the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumours. As of 18 February 2014, a total of 198 patients have entered into this study of which 177 had received MEDI4736 at 10 mg/kg given every 2 weeks (Q2W). The most frequently reported (≥10% of subjects) 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.

Grade 3 or higher treatment-emergent AEs were noted in 44/177 subjects (24.9%). These events occurring in more than 1 subject included dyspnoea (9 subjects); dehydration

(4 subjects); abdominal pain, fatigue, sepsis, increased AST and increased gamma glutamyltransferase (3 subjects); and hyperbilirubinemia, back pain, pulmonary embolism, respiratory failure and hypotension (2 subjects each). The Grade 3 or higher treatment-emergent AEs that were considered by the Investigator to be related to MEDI4736 were increased AST (2 subjects), and hypothyroidism, vomiting, fatigue, infusion related reaction, troponin, dehydration and arthralgia (1 subject each).

Treatment-related AEs were reported for 52/177 subjects (29.4%). The most frequently reported (2 or more subjects) treatment-related AEs (all grades) were fatigue (11.3%); nausea (5.6%); dyspnoea (4.0%); diarrhoea, vomiting and pyrexia (3.4% each); myalgia (2.8%); hypothyroidism, decreased appetite, dizziness, cough, pruritus and rash (2.3% each), abdominal pain, increased AST and arthralgia (1.7% each); and asthenia, influenza-like illness, oedema peripheral, increased ALT, headache and dry skin (1.1% each). No DLTs have been reported.

Serious adverse events (SAEs; not necessarily related to MEDI4736) that were reported in this study and observed in 3 or more subjects at 10 mg/kg Q2W include dyspnoea (2.8%), dehydration (2.3%), abdominal pain (1.7%) and sepsis (1.7%). Treatment-related SAEs noted at the 10mg/kg Q2W dosing schedule were observed in 3 patients: pneumonitis, pleural effusion, arthralgia, right-hand weakness and rule out cord compression.

Of the 198 subjects enrolled, 28 subjects have died (25 subjects treated with MEDI4736 10 mg/kg Q2W, and 1 subject in each of the 0.1, 0.3 and 3.0 mg/kg Q2W cohorts). No subjects died on treatment. None of the deaths were considered related to MEDI4736 by the Investigator and all deaths were “due to disease” with the exception of 1 subject (cause of death was reported as “disease under treatment”).

Of the 177 subjects treated with MEDI4736 10 mg/kg Q2W, 77 have had at least one post-baseline disease assessment as of 18 February 2014. No subjects had a CR. Four subjects (5.2%) had a best response of PR (unconfirmed) assessed by irRC: 1 subject with advanced cutaneous melanoma, 1 subject with squamous cell carcinoma of the head and neck, 1 subject with squamous NSCLC, and 1 subject with non-squamous NSCLC. In addition, 36 subjects (46.8%) had stable disease (SD), 20 subjects (26.0%) had confirmed PD, 14 subjects (18.2%) had unconfirmed PD, and 3 subjects (3.9%) were not evaluable.

Twelve of the 15 subjects in the 0.1, 0.3, 1.0 mg/kg, and 3.0 mg/kg Q2W dose-escalation cohorts had at least one post-baseline disease assessment as of 18 February 2014. Two subjects in each of the 0.3 and 1.0 mg/kg cohorts had a best response of PR (3 confirmed and 1 unconfirmed) assessed by irRC (Wolchok et al 2009). All 6 subjects in the 15 mg/kg Q3W cohort had at least one post-baseline disease assessment as of 18 February 2014. No subjects had CR or PR, 4 subjects had a best response of SD, 1 subject had confirmed PD, and 1 subject had unconfirmed PD.

### 1.1.6 Safety pharmacology summary

Refer to the latest version of the IB for the latest information on identified and potential risks associated with MEDI4736.

There are a number of potential/possible risks based on the mechanism of action of MEDI4736 and related molecules including immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity, endocrinopathy, and neuropathy.

A hypothetical risk exists for agents that activate the immune system by delivering agonistic signals through activating receptors, such as CD28 (Suntharalingam et al 2006). Such agents have an increased potential to trigger systemic, nonspecific activation of T-cells since they can exert their effects in the absence of any antigen-specific T-cell receptor signals. In contrast, agents that act via antagonism of an inhibitory pathway modulate an existing antigen-specific T-cell receptor signal and have a limited potential to drive systemic, nonspecific activation of T-cells. This is exemplified clinically by molecules targeting CTLA-4 and PD-1, which are not associated with acute, severe adverse effects, such as a cytokine storm (Berger et al 2008, Brahmer et al 2010, Wolchok et al 2010). Like these molecules, MEDI4736 antagonizes an inhibitory receptor (PD-L1). As such, in the absence of an antigen-specific T-cell receptor signal, inhibition of function of PD-L1 is not anticipated to elicit any response. This expectation is supported by published data showing no effect for anti-PD-L1 antibodies in the absence of a T-cell receptor stimulus (Dong et al 2003).

To assess directly the potential of MEDI4736 to induce a release of cytokines, cytokine release assays were conducted in human whole blood. MEDI4736 did not induce release of any cytokine from any donor at any concentration tested. These results support that, consistent with its mechanism of action as a PD-L1 antagonist, MEDI4736 is not expected to induce acute cytokine release in humans. Nevertheless, the MEDI4736 FTIH study design took into account the unlikely possibility of a cytokine release event by having a low starting dose, extensive monitoring, and cytokine sampling.

### 1.1.7 Genetic data

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

## 1.2 Research hypothesis

The research hypothesis for this study is: MEDI4736 (10 mg/kg Q2W via iv infusion) will show improved efficacy compared with placebo when given as sequential therapy to patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

This will be assessed via the primary objective of this study, which is to assess the efficacy of MEDI4736 treatment compared with placebo in terms of OS and progression free survival (PFS). Secondary efficacy objectives include evaluation of the proportion of patients alive at 24 months from randomisation (OS24), ORR, DoR, the proportion of patients alive and

progression free at 12 months from randomisation (APF12) and the proportion of patients alive and progression free at 18 months from randomisation (APF18), the time from randomisation to second progression (PFS2), and time to death or distant metastasis (TTDM). Other secondary objectives include an assessment of safety and tolerability, MEDI4736 PK exposure, immunogenicity and patient reported outcomes (PRO). Exploratory objectives are also included.

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

## 1.3 Rationale for conducting this study

The rationale for combining chemotherapy and radiotherapy is to combine the benefits of radiotherapy in terms of local regional control with the benefits of chemotherapy in terms of reducing the risks of metastatic disease. With concurrent chemoradiation (cCTRT) there is the potential for chemotherapy, given during a course of radiotherapy, to enhance the effectiveness of radiotherapy (ie, radiosensitisation) (O'Rourke et al 2010).

For patients with unresectable Stage IIIA or Stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone and cCTRT is superior to sequential therapy (NCCN Guidelines 2014). Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide, cisplatin/vinblastine or carboplatin/paclitaxel (TAXOL®). For non-squamous NSCLC other cCTRT regimens include cisplatin/pemetrexed (ALIMTA®) (NCCN Guidelines 2014). The guidelines for the treatment of patients with unresectable Stage IIIA or Stage IIIB NSCLC in Europe (Vansteenkiste et al 2013) and Japan (Saijo et al 2010) are in line with those used in the US.

However, the majority of patients inevitably progress (PFS is usually short; approximately 8 months) and 5-year OS is approximately 15% (Butts et al 2014).

Whilst advances have been made in improving survival from Stage III NSCLC by optimising local control, evidence suggests that cCTRT does not reduce the risk of distant relapse. With fewer cycles and, in some cases, lower doses of chemotherapy being delivered in the concurrent setting, several studies have assessed whether delivering induction or consolidation treatment will improve survival. A pooled analysis of 41 Phase II/III trials confirmed that there remains no evidence to suggest that consolidation chemotherapy after cCTRT improves survival for patients with Stage III NSCLC and current guidelines continue to recommend cCTRT alone for the treatment of inoperable Stage III NSCLC (Bayman et al 2014). There is still therefore a significant unmet medical need for additional treatment options for use in this patient population to improve on PFS and OS (see Section 1.1.1).

The sequential/consolidation setting post cCTRT may be ideal to evaluate the efficacy of immunotherapy, which is aimed at boosting the ability of the patient immune system to eliminate cancer cells.

Tumours that are poorly immunogenic or that have become immunosuppressive can likely be made immunogenic through administration of pro-immunogenic therapies designed to

increase antigen release from the cancer cell. Potential priming agents for immunotherapy agents include chemotherapy and radiotherapy. Some cytotoxic therapies, such as anthracyclines or ionizing radiation, promote 'immunogenic cell death', which includes the release of 'danger' molecules from tumour cells such as calreticulin, high mobility group protein B1 and adenosine triphosphate. These danger molecules polarize dendritic cells towards a pro-inflammatory phenotype and increase priming towards T helper 1 anti-tumour T-cells and away from regulatory T-cells (Vanneman and Dranoff 2012). Additionally, a recent Phase II trial in patients with Stage IIIb/IV NSCLC or extensive-disease small-cell lung cancer investigated whether the anti-CTLA-4 agent ipilimumab could be given safely in combination with standard chemotherapy (carboplatin–paclitaxel) as well as whether it would be optimal to initiate ipilimumab at the same time as chemotherapy, or after 2 cycles of treatment. The results from this Phase II trial showed that the combination was reasonably well-tolerated, and that a 'phased regimen' in which immunotherapy began after chemotherapy resulted in substantially improved PFS compared with carboplatin–paclitaxel alone. While this study did not actively investigate dosing effects, the data show that the clinical effects of administering immunotherapy in combination with chemotherapy are strongly dependent on the sequencing of treatment (Drake 2012).

The therapeutic application of ionizing radiation has been largely based on its cytocidal power combined with the ability to selectively target tumours. Radiotherapy effects on survival of cancer patients are generally interpreted as the consequence of improved local control of the tumour, directly decreasing systemic spread. Experimental data from multiple cancer models have provided sufficient evidence to propose a paradigm shift, whereby some of the effects of ionizing radiation are recognised as contributing to systemic antitumour immunity. Interventions such as radiotherapy that promote the release of tumour neoantigens in an immunogenic way, together with strategies to overcome dominant immunosuppressive pathways, offer opportunities to recover effective immune reactivity (Formenti and Demaria 2013). By coupling release and/or expression of new antigens with immune adjuvant-like effects, radiotherapy engages both the innate and adaptive arms of the immune system, with the potential to convert the irradiated cancer into an in situ vaccine that elicits tumour-specific T-cells. Once vaccinated, the host is endowed with immune memory, a powerful weapon active against synchronous non-irradiated tumour sites and potentially against cancer cells that emerge from dormancy during the life of the host. Such immune memory may explain radiotherapy's repercussions on the final outcome of irradiated patients. Radiotherapy's effect on local tumour control is associated with an effect on metastatic recurrence and eventual cancer survival. For instance, two meta-analyses of prospective, randomised trials in breast cancer demonstrated a direct contribution of adjuvant radiotherapy to patients' long-term survival. The effect was independent of the stage and extent of surgery (Formenti and Demaria 2013).

In addition, the clinical observation of the abscopal effect of tumour regression outside the irradiated field may be a result of radiation induced antigen and cytokine release and the subsequent immune response against the tumour. Anecdotes have been published describing the abscopal effect with ipilimumab. In addition it has been shown than fractionated radiotherapy induces an abscopal effect when in combination with an anti–CTLA-4 antibody

in two non-clinical carcinoma models (Dewan et al 2009). In syngeneic mice models of cancer the combination of radiotherapy and anti-CTLA-4 resulted in successful T-cell-mediated antitumour responses, whereas anti-CTLA-4 treatment by itself was ineffective. Inhibition of early lung metastases and responses of bulky tumours outside the radiation field were observed in mice with established poorly immunogenic mammary and colorectal carcinomas (Formenti and Demaria 2013). Initial evidence in lung and breast carcinoma and glioma suggests that antibodies that target other checkpoint receptors on T-cells and/or co-stimulatory molecules such as CD137 can also be successfully combined with radiotherapy (Formenti and Demaria 2013). Both chemotherapy and radiotherapy can up-regulate the expression of PD-L1 (Zhang et al 2008b, Deng et al 2014) due to the release of cytokines and other inflammatory molecules, which could therefore make such tumours sensitive to a PD-L1 directed therapy.

MEDI4736, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and therefore enhance the cytotoxic activity of anti-tumour T-cells. This hypothesis is supported by emerging clinical data from other monoclonal antibodies targeting the PD-L1/PD-1 pathway (see Section 1.1.2), which provide early evidence of clinical activity and a manageable safety profile superior to the anti-CTLA-4 class.

## 1.4 Benefit/risk and ethical assessment

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

### 1.4.1 Unmet need and potential role of immunotherapies in NSCLC

Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status and unresectable Stage III NSCLC is platinum-based doublet chemotherapy and radiotherapy administered with curative intent. A meta-analysis of concurrent versus sequential chemoradiotherapy showed better outcomes with concurrent therapy, but even with concurrent chemoradiotherapy 5-year OS is only approximately 15% (Butts et al 2014).

Whilst advances have been made in improving survival from Stage III NSCLC by optimising local control, evidence suggests that cCTRT does not reduce the risk of distant relapse. With fewer cycles and, in some cases, lower doses of chemotherapy delivered in the concurrent setting, several studies have assessed whether delivering induction or consolidation treatment will improve survival. A pooled analysis of 41 Phase II/III trials confirmed that there remains no evidence to suggest that consolidation chemotherapy after cCTRT improves survival for patients with Stage III NSCLC and current guidelines continue to recommend cCTRT alone for the treatment of inoperable Stage III NSCLC (Bayman et al 2014). Given the lack of persuasive evidence for an active comparator, the use of a placebo comparator is justified in the proposed sequential/consolidation setting in this study.

The sequential/consolidation setting post-cCTRT may be ideal to evaluate the efficacy of immunotherapy, which is aimed at boosting the ability of the patient immune system to eliminate cancer cells. Chemoradiotherapy often induces initial tumour shrinkage followed by eventual PD as the tumours find mechanisms to bypass the chemoradiotherapy-induced growth inhibition. The initial tumour shrinkage observed in some patients following chemoradiotherapy is the result of cell death and tumour damage.
Chemoradiotherapy-induced cell death can enhance the ability of the immune system to recognise and respond to the tumour through enhanced antigen release and presentation which, in turn, aids in the priming of immune cells to recognise and eliminate tumour cells. Therefore, triggering or augmenting an antigenic antitumour response with chemoradiotherapy and combining or following this treatment with anti-PD-L1 therapy, which acts to preserve ongoing immune responses by blocking an immunosuppressive signal theoretically may result in enhanced antitumour activity by improving local control and decreasing systemic spread.

### 1.4.2 Summary of MEDI4736 data and potential benefits and risks

MEDI4736, a human monoclonal antibody directed against human PD-L1, may offer benefit to this patient population. MEDI4736 has a high affinity for human PD-L1 and is able to completely block the interaction of recombinant human PD-L1 with both recombinant human PD-1 and recombinant human CD80 in a biochemical assay. In vitro, MEDI4736 enhances the proliferation and activation of primary human T-cells cultured in the presence of rPD-L1.

Nonclinical studies demonstrate that MEDI4736 inhibits tumour growth in mouse xenograft models. This activity is shown to be dependent upon the presence of human T-cells, supporting the hypothesis that PD-L1 blockade can enhance anti-tumour immune response. No MEDI4736-associated risks have been reported in nonclinical safety studies in cynomolgus monkeys. Please refer to Section 1.1.5 and the current IB for clinical experience with MEDI4736.

Important potential risks associated with MEDI4736, as with the administration of any foreign protein and/or other biologic agents, 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.

### 1.4.3 Summary of potential benefits and risks of other immunotherapy agents

Other monoclonal antibodies targeting the PD-1/PD-L1 pathway are currently in clinical development. Among the most frequent treatment-related AEs noted in 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 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 MEDI4736, including other monoclonal antibodies 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). The experience to date with anti-PD-1/PD-L1 monoclonal antibodies suggests that these agents can provide significant clinical activity with a manageable safety profile that is superior to that of the anti-CTLA-4 class.

### 1.4.4 Summary benefit: risk statement

In summary, the potential for clinical benefit associated with inhibition of the PD-1/PD-L1 pathway, supported by objective responses observed in earlier studies in patients with NSCLC, outweighs the known and potential risks based on the AEs reported in patients treated with MEDI4736 and other PD-1/PD-L1 inhibitors. Thus, the benefit/risk assessment, favours the conduct of this proposed study.

The safety of patients in this study will be assessed by an Independent Data Monitoring Committee (IDMC) via ongoing safety assessments and formal interim analyses of safety data at 3 months, 6 months and then at least every 6 months thereafter.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| Primary Objective: | Outcome Measure: |
|---|---|
| To assess the efficacy of MEDI4736 treatment compared with placebo in terms of OS and PFS | OS<br>PFS using BICR assessments according to RECIST 1.1[a] |

a The co-primary analysis of PFS will be based on programmatically derived PFS using BICR assessments according to RECIST 1.1. See Section 12.2.2 for further details.

BICR Blinded Independent Central Review; OS Overall survival; PFS Progression free survival; RECIST Response Evaluation Criteria In Solid Tumours.

## 2.2 Secondary objectives

| Secondary Objective: | Outcome Measure: |
|---|---|
| To further assess the efficacy of MEDI4736 compared with placebo in terms of: OS24, ORR, DoR, APF12, APF18, PFS2 and TTDM | OS24<br>ORR using BICR assessments according to RECIST 1.1a<br>DoR using BICR assessments according to RECIST 1.1[a]<br>APF12 and APF18 using BICR assessments according to RECIST 1.1[a]<br>PFS2 as defined by local standard clinical practice<br>TTDM using BICR assessments according to RECIST 1.1[a] |
| To assess the safety and tolerability profile of MEDI4736 compared with placebo | AEs, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, haematology and urinalysis |
| To assess the PK of MEDI4736 | Concentration of MEDI4736 in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling) |
| To investigate the immunogenicity of MEDI4736 | ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed]) |
| To assess symptoms and health-related quality of life in patients treated with MEDI4736 compared with placebo 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)<br>LC13: Time to symptom deterioration (dyspnoea, cough, haemoptysis, chest pain, arm/shoulder pain, other pain)<br>Changes in World Health Organization Performance Status will also be assessed |

a Analysis of ORR and DoR will be based upon BICR assessment according to RECIST 1.1. See Sections 12.2.3 and 12.2.5 for further details.
Note: Prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

ADA Anti-drug antibody; AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomisation; APF18 Proportion of patients alive and progression free at 18 months from randomisation; BICR Blinded Independent Central Review; 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; OS24 Proportion of patients alive at 24 months from randomisation; PFS2 Time from randomisation to second progression; PK Pharmacokinetic(s); QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumours; TTDM Time to death or distant metastasis.

## 2.3 Exploratory objectives

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To explore irRC criteria as an assessment methodology for clinical benefit of MEDI4736 compared with placebo by BICR | PFS and ORR using BICR assessments according to irRC |
| To investigate the relationship between MEDI4736 PK exposure and clinical outcomes, efficacy, AEs and/or safety parameters, if deemed appropriate | A graphical and/or a data modelling approach will be used to analyse MEDI4736 PK exposure and the relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate |
| To describe and evaluate resource use associated with MEDI4736 treatment and underlying disease | Health resource utilisation measures including hospitalisation, outpatient visits, or emergency department visits |
| To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L | The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data |
| To investigate the relationship between a patient's PD-L1 expression and spatial distribution within the tumour microenvironment and efficacy outcomes with MEDI4736 | Tumoural expression of PD-L1 and spatial distribution within the tumour microenvironment relative to efficacy outcomes (OS, PFS and ORR) |
| To collect blood and tissue samples for analysis of peripheral and tumoural biomarkers | Biomarker analysis of blood and tissue to assess exploratory markers which may include but is not limited to: immune cell gene expression profiles within the peripheral and tumoural compartments, the presence of IFN-γ tumour necrosis factor-α, IL-2, IL-6, IL-10, IL-8, and IL-12 as well as antibodies against tumour, self, or viral antigens, expression of PD-L1 and the number and phenotype of immune cells such as T-cells |
| To explore the relationship(s) between a patient's biomarker status and MEDI4736 PK exposure and clinical outcomes before and after treatment | Biomarker status before and after treatment and MEDI4736 PK exposure and relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate |
| To explore potential biomarkers in residual biological samples (eg, tumour, plasma and/or serum), which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to MEDI4736 treatment | Correlation of biomarkers with response to MEDI4736 treatment and/or the progression of cancer |
| To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study drugs and/or susceptibility to disease (optional) | Correlation of polymorphisms with variation in PK, PDx, safety or response parameters observed in patients treated with MEDI4736 and/or susceptibility to disease |

AE Adverse event; BICR Blinded Independent Central Review; EQ-5D-5L EuroQoL 5 dimension, 5 level health state utility index; IFN Interferon; IL Interleukin; irRC Immune-related response criteria; ORR Objective response rate; PD-L1 Programmed death ligand 1; PDx Pharmacodynamic(s); PFS Progression free survival; PK Pharmacokinetic(s); T-cell T lymphocyte.

PD-L1 expression determined by immunohistochemistry will be reported in the Clinical Study Report (CSR). Other exploratory biomarker and PGx research will be reported outside the CSR. Data relating to the exploratory objectives of PRO and Health Related Quality of Life (HRQoL) will be reported in the CSR.

# 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, double-blind, placebo-controlled, multi-centre study assessing the efficacy and safety of MEDI4736 compared with placebo as sequential therapy in male and female patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

Approximately 880 patients with locally advanced, unresectable non-small cell lung cancer (NSCLC; Stage III) will be recruited and 702 patients randomised at 260 to 330 sites in Australia, Asia, Europe, North and South America and South Africa. These patients will be in complete response (CR), PR, or have SD following definitive, platinum-based, concurrent chemoradiation therapy.

Patients must have histologically- or cytologically-documented NSCLC who present with locally advanced, unresectable (Stage III) disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology]).

Patients will be randomised in a 2:1 ratio (MEDI4736 to placebo) to 1 of 2 arms:

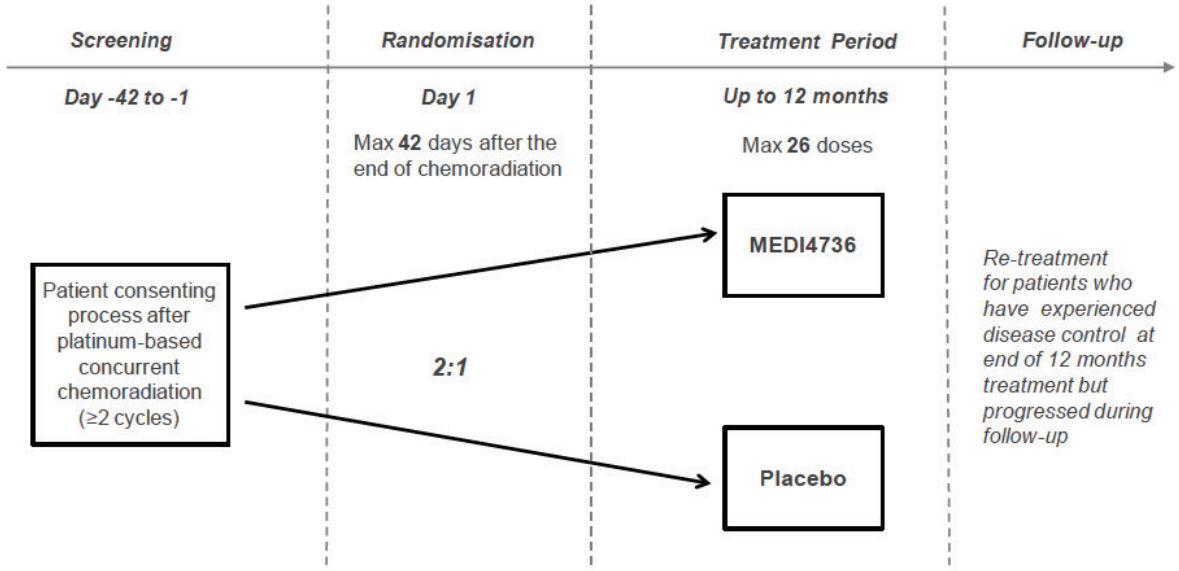
- MEDI4736 (10 mg/kg Q2W iv for up to 12 months).
- Placebo (matching placebo for infusion Q2W iv for up to 12 months).

Randomisation will be stratified by: age at randomisation (<65 versus ≥65 years of age), sex (male versus female), and smoking history (smoker versus non-smoker). Patients must not have progressed following definitive, platinum-based, concurrent chemoradiation therapy; radiation therapy must be completed within 1 to 42 days prior to randomisation in the study (the last dose of radiation therapy is defined as the day of the last radiation treatment session). For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy. For those patients randomised to the placebo arm no cross-in to the MEDI4736 arm is permitted and similarly those patients randomised to the MEDI4736 arm no cross-in to the placebo arm is permitted.

Administration of study drug (ie, investigational product MEDI4736 or placebo) will commence on Day 1 following randomisation to MEDI4736 or placebo after confirmation of eligibility and will continue on a Q2W schedule for a maximum duration of 12 months (maximum of 26 doses, last dose at Week 50). Study drug should be discontinued prior to 12 months if there is confirmed PD (unless the Investigator considers the patient continues to receive benefit from the study drug), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue study drug occur.

The study design is shown in figure form in Figure 1.

**Figure 1 Study design schema**




Tumour assessments using computed tomography (CT)/magnetic resonance imaging (MRI) will be performed at the times specified in Table 1, Table 2 and Table 3. Response Evaluation Criteria In Solid Tumours 1.1 measurements (using BICR assessments) will be used to derive the co-primary variable of PFS and secondary variables of ORR, DoR, APF12, and APF18. Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Patients with no evidence of disease at follow-up in the absence of new lesions will be assigned a response of no evidence of disease (NED). Blinded Independent Central Review (BICR) will be conducted.

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.

There will be up to 4 DCO time points in the study. The first analysis DCO will occur when it is expected that 367 PFS events have occurred (52% maturity, approximately 30 months after the first patient is randomised). The second analysis DCO will occur at the time of the primary PFS analysis when it is expected that 458 PFS events have occurred (65% maturity,

approximately 36 months after the first patient is randomised), and the first OS interim analysis will be conducted at the same time (with approximately 285 events, 41% maturity). The third analysis DCO will occur at the time of the second OS interim analysis when it is expected that 393 OS events have occurred (56% maturity, approximately 47 months after the first patient is randomised). The fourth analysis DCO will occur at the time of the primary OS analysis when it is expected that 491 OS events have occurred (70% maturity, at approximately 62 months). Further analyses for that particular endpoint may occur based on the needs for long term follow-up with more mature data. See Section 12.3 for further details.

Sensitivity analyses will be performed on PFS and ORR using Investigator tumour data based on all scans upon RECIST 1.1 and site Investigator tumour data based on all scans upon RECIST 1.1 modified for confirmation of progression. Exploratory analysis of PFS and ORR will also be performed for data obtained from the BICR on a subset 250 evaluable patients using irRC. See Section 6.3 and Appendix F for further information regarding RECIST tumour assessments in this study.

The study flow chart is presented in Figure 2.

The schedule of study procedures at Screening and during the Treatment Period is presented in Table 1. The schedule of study procedures during follow-up for patients who have completed the Treatment Period and achieved disease control (until confirmed PD) and patients who have discontinued study drug due to toxicity or a reason other than confirmed PD is presented in Table 2. The schedule of study procedures during follow-up for patients who have discontinued study drug due to confirmed PD is presented in Table 3. The schedule of study procedures for all patients during long-term follow up is presented in Table 11.

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

Details of the PGx component of the study (relating to DNA) are provided in Appendix D.

*End of Analysis Portion of Study*

Once the planned statistical analyses have been performed for both the primary analysis of PFS and OS endpoints of the study, data collection will be reduced. Please refer to Section 9.5.1 for more information.

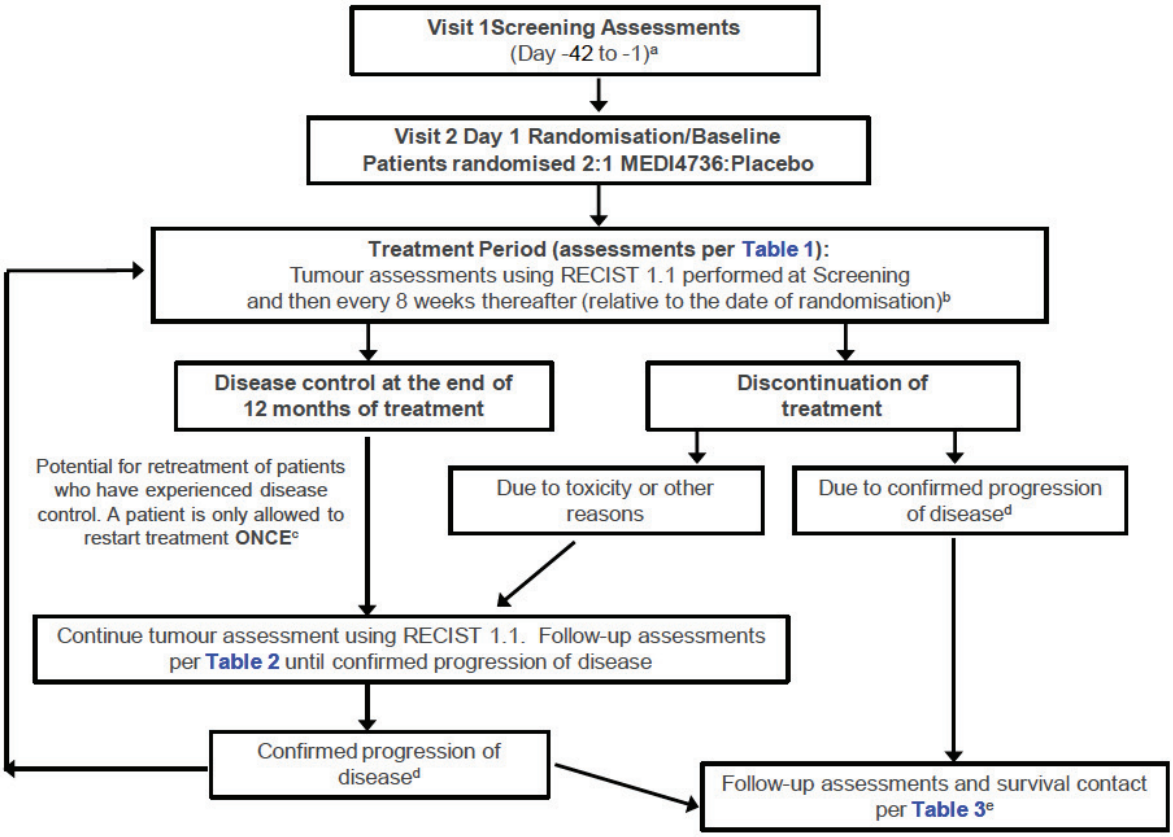
Once the final DCO of the study for long-term follow-up has been reached, patients in OS and PFS follow-up will be considered to have completed the study. At the time of the final DCO (anticipated to be approximately 5 years following the last patient randomised) any patient who is still in progression free follow up will have been progression free for approximately 5 years following the start of their chemoradiation; as such, they will be considered cured and will no longer be considered eligible for re-treatment within this protocol. Those patients who are still actively in re-treatment, and continuing to receive clinical benefit, will have the option to continue on study drug on an alternate rollover or extension study. Please refer to Section 9.5.2 for more information.

**Independent Data Monitoring Committee**

An IDMC will be convened and will meet approximately 3 months after the study has started, or once 75 patients have been randomised whichever occurs first, to review safety assessments and make recommendations to continue, amend, or stop the study the study based on safety findings. The first two efficacy analyses will also be assessed by the IDMC. The committee will then meet again 3 months later and then at least every 6 months thereafter up to the decision to unblind the study. All patients who receive a dose of study drug 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. In addition, the IDMC will review the unblinded interim analysis summaries of efficacy data.

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.

**Figure 2 Study flow chart**




[a] Screening assessments can be performed in a step-wise process. The baseline tumour assessment is part of the screening procedures and should be performed within 0 to 42 days after the end of chemoradiation therapy and before the start of study drug. For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy.

[b] Disease progression needs to be confirmed, 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 drug 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 and re-treatment 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.

[c] Patients who achieve and maintain disease control (ie, CR, PR, no evidence of disease, or SD) through to the end of the 12-month treatment period may restart and continue 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 still meet all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to treatment. To restart study drug the patient must not have received an intervening systemic anti-cancer therapy post study drug discontinuation. Patients should have a baseline tumour assessment within 28 days of restarting study drug, all further scans should occur every 8 weeks (relative to the date of restarting study drug). Patients who continue to receive re-treatment after the final DCO should receive tumour assessment scans and other assessments as per local clinical 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 MEDI4736 TMGs (refer to Section 5.5.3).

[d] Patients with confirmed PD that 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 during the initial treatment period but for as long as the Investigator judges that they are gaining clinical benefit if they are a re-treatment patient. 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 re-treatment as specified in Section 4.3. The same exceptions as noted in footnote b apply. Patients will follow the assessments in Table 1 including tumour assessments every 8 weeks (relative to the date of randomisation) until study drug is stopped. Patients who continue to receive re-treatment after the final DCO should receive tumour assessment scans and other assessments as per local clinical 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 MEDI4736 TMGs (refer to Section 5.5.3). Study drug should be discontinued if there is confirmed PD following a previous response (PR or CR) to study drug.

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

Note: At final DCO for the study, patients who are receiving study drug can either choose to discontinue from the study or where the Investigator judges that patients are gaining clinical benefit, patients may continue to receive study drug. For patients who do continue to receive study drug beyond the time of the final DCO, Investigators must continue to report all 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 DCO are to be followed up at the Investigator's discretion and per local standard of care.

AE Adverse event; BICR Blinded Independent Central Review; CR Complete response; DCO Data cut-off; PD Progression of disease; PR Partial response; RECIST Response Evaluation Criteria In Solid Tumours; SAE Serious adverse event; SD Stable disease.

**Table 1 Schedule of study procedures: 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.) | **Screening** | **All assessments to be performed pre-infusion unless stated otherwise** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Randomisation** | | | | | **Every 2 Weeks** | **Every 4 Weeks** | **Every 8 Weeks** |
| **Day** | **-42 to -1** | **1** | **15** | **29** | **43** | **57** | | **Day 1 of the week** | |
| **Week** | **-6 to -1** | **0** | **2** | **4** | **6** | **8** | **10, 12, 14, 16 etc** | **12, 16, 20, 24, 28, etc** | **16, 24, 32, 40 and 48** |
| | | | **(±3 days)** | | | | | | **(±7 days)** |
| Written informed consent/assignment of patient identification number (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 | | | | | | | | |
| Verify eligibility criteria | X | X | | | | | | | |
| Randomisation | | X | | | | | | | |
| Demography and history of tobacco and alcohol use | X | | | | | | | | |
| Patient questionnaires (patient reported outcomes) | X | X | | X | | X | | | X |
| Health resource use | | X | | X | | X | | X | |
| Medical and surgical history (including all treatments for NSCLC) | X | | | | | | | | |
| Hepatitis B and C; HIV | X | | | | | | | | |
| Urine hCG or serum βhCG | X | X | X | X | X | X | X | | |
| **Kit assignment and MEDI4736 or placebo administration** | | X | X | X | X | X | X (last dose Week 50) | | |
| Physical examination | X | X | X | X | X | X | | X | |
| Vital signs (BP, pulse [pre- and post-infusion], respiratory rate, temperature and oxygen saturation; see Section 6.4.8) | X | X | X | X | X | X | X | | |

**Table 1 Schedule of study procedures: 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.) | **Screening** | **All assessments to be performed pre-infusion unless stated otherwise** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Randomisation** | | | | | **Every 2 Weeks** | **Every 4 Weeks** | **Every 8 Weeks** |
| **Day** | **-42 to -1** | **1** | **15** | **29** | **43** | **57** | | **Day 1 of the week** | |
| **Week** | **-6 to -1** | **0** | **2** | **4** | **6** | **8** | **10, 12, 14, 16 etc** | **12, 16, 20, 24, 28, etc** | **16, 24, 32, 40 and 48** |
| | | | **(±3 days)** | | | | | | **(±7 days)** |
| Weight | X | X | | X | | X | | X | |
| Height | | X | | | | | | | |
| Electrocardiogram[a] | X | As clinically indicated | | | | | | | |
| Adverse event/serious adverse event assessment | X | X | X | X | X | X | X | | |
| Concomitant medications | X | X | X | X | X | X | X | | |
| World Health Organization performance status | X | X | X | X | X | X | X | | |
| Serum chemistry[b] | X | X | X | X | X | X | X | | |
| Amylase, lipase (where available)[b] | X | X | | X | | X | | X | |
| Thyroid function tests (TSH and T3 and T4) | X | X | X | X | X | X | | X | |
| Haematology[b] | X | X | X | X | X | X | X | | |
| Urinalysis[c] | X | X | | X | | X | | X | |
| Coagulation parameters[d] | X | | | | | | | | |
| PK assessment[e] | | X (pre and EOI) | | | | X (pre) | | | X (only at Week 24 [pre and EOI] and at Week 48 [pre])) |

**Table 1 Schedule of study procedures: 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.) | **Screening** | **All assessments to be performed pre-infusion unless stated otherwise** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Randomisation** | | | | | **Every 2 Weeks** | **Every 4 Weeks** | **Every 8 Weeks** |
| **Day** | **-42 to -1** | **1** | **15** | **29** | **43** | **57** | | **Day 1 of the week** | |
| **Week** | **-6 to -1** | **0** | **2** | **4** | **6** | **8** | **10, 12, 14, 16 etc** | **12, 16, 20, 24, 28, etc** | **16, 24, 32, 40 and 48** |
| | | | **(±3 days)** | | | | | | **(±7 days)** |
| Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation)[e] | | X (pre) | | | | X (pre) | | | X (only at Week 24 [pre] and at Week 48 [pre]) |
| sPD-L1 concentration (to assess target engagement)[e] | | X | | | | X (pre) | | | X (only at Week 24 [pre] and at Week 48 [pre]) |
| Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) | | X | | X | | | | X (only at Week 12) | |
| miRNA/mRNA (to examine immune cell gene expression profiles in circulation) | | X | | | | X | | | X (only at Week 48) |
| Archival tumour tissue sample | X | | | | | | | | |
| Tumour biopsy (optional) (see Section 6.7) | X | | | | | | | | |
| PGx sample (optional [DNA element]) | X | | | | | | | | |
| Tumour assessment (CT or MRI)[f,g,h] | X | | | | | X[i] | | | X |

[a] Electrocardiograms are to be performed in triplicate at Screening. ECGs should be performed at other time if clinically indicated. Any clinically significant abnormalities detected require triplicate ECG results.

[b] Results for urea and electrolytes, full blood count and liver function tests must be available before commencing an infusion. 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 and as clinically indicated. Creatinine clearance, magnesium, amylase, lipase, and uric acid tested at Screening and every 4 weeks thereafter.

[c] Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

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

[e] **For ADA, sPD-L1:** These assessments will be performed pre-infusion on Day 1, Week 8, Week 24 and Week 48. **PK samples** should be collected on Day 1, Week 8, Week 24 and Week 48. Only on Day 1 (randomisation visit) and at Week 24 before and after the infusion. At Week 8 and Week 48, only a pre-dose sample will be collected. Pre-dose samples can be taken within 60 minutes before infusion and the end-of-infusion samples within 10 minutes after the end of infusion. **Circulating soluble factors** assessment will be performed pre-infusion on Day 1, Week 4 and Week 12. **For miRNA/mRNA** the assessment will be performed pre-infusion on Day 1, Week 8 and Week 48.

[f] 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 is part of the screening procedures and should be performed within 0 to 42 days after the end of chemoradiation therapy and no more than 28 days before the start of study drug. For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy. Follow-up assessments will be performed every 8 weeks 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 initial 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 and re-treatment 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.

[g] Patients who achieve and maintain disease control (ie, CR, PR, NED, or SD) through to the end of the 12-month 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 still meet all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to study drug. To restart study drug the patient must not have received an intervening systemic anti-cancer therapy post study drug discontinuation. Patients should have a baseline tumour assessment within 28 days of restarting study drug, all further scans should occur every 8 weeks (relative to the date of restarting study drug), or, if they receive re-treatment after the final DCO, patients should receive tumour assessment scans and other assessments as per local clinical 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 durvalumab in order to manage AEs in accordance with the durvalumab TMGs (refer to Section 5.5.3).

[h] Patients with confirmed PD who continue to receive study drug at the discretion of the Investigator (following consultation with the sponsor) can receive study drug for as long as the Investigator judges that they are gaining clinical benefit. Patients will have scans every 8 weeks (relative to the date of randomisation) while on study drug, or, if they receive re-treatment after the final DCO, patients should receive tumour assessment scans and other assessments as per local clinical 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 durvalumab in order to manage AEs in accordance with the durvalumab TMGs (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 progression of disease (PD) following a previous response (PR or CR) to study drug.

[i] At Week 8 the allowed window for the tumour assessment is ±7 days.

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: Patients should commence study drug as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS system) and no later than 24 hours after randomisation.

Note: For 're-treatment' patients who go on to have a 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, and sPD-L1 assessments which do not need to be collected a second time.

ADA Anti-drug antibody; APTT Activated partial thromboplastin time; BP Blood pressure; CT Computed tomography; ECG Electrocardiogram; EOI End of infusion; hCG Human chorionic gonadotropin; HIV Human immunodeficiency virus; INR International normalised ratio; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NED No evidence of disease; NSCLC Non-small cell lung cancer; PD Progression of disease; PGx Pharmacogenetic(s); PK Pharmacokinetic(s); RECIST Response Evaluation Criteria In Solid Tumours; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

**Table 2** **Schedule of study procedures: follow-up for patients who have completed the treatment period for study drug and achieved disease control (until confirmed progression of disease) and patients who have discontinued study drug due to toxicity or a reason other than confirmed progression of disease**

| Evaluation | Time Since Last Dose of Study Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months Thereafter (±2 weeks)[d] |
| | 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 of treatment,** patient questionnaires and information related 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.<br>For patients who **discontinue study drug due to toxicity or a reason other than confirmed PD**, patient questionnaires and information related 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 1), then every 12 weeks thereafter until confirmed PD by RECIST 1.1 by investigational site review. | | | | | | | |
| Physical examination | X | | | | | | | |
| Vital signs (BP, pulse, respiratory rate, temperature, oxygen saturation; see Section 6.4.8) | X | | | | | | | |
| Weight | X | | | | | | | |
| AE/SAE assessment | X | X | X | | | | | |
| Concomitant medications | X | | | | | | | |
| World Health Organization performance status[a] | X | X[a] | X | X[a] | X[a] | X[a] | X[a] | X[a] |
| Subsequent anticancer 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 | X | X | | | | X |
| Serum chemistry | X | X | X | | | | | |

**Table 2** **Schedule of study procedures: follow-up for patients who have completed the treatment period for study drug and achieved disease control (until confirmed progression of disease) and patients who have discontinued study drug due to toxicity or a reason other than confirmed progression of disease**

| Evaluation | Time Since Last Dose of Study Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months Thereafter (±2 weeks)[d] |
| | 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 assessment | | | X | | | | | |
| Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) | | | X | | X | | | |
| sPD-L1 concentration (to assess target engagement) | | | X | | | | | |
| Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) | X | | | | X | | | |
| miRNA/mRNA (to examine immune cell gene expression profiles in circulation) | X | | | | | | | |

**Table 2 Schedule of study procedures: follow-up for patients who have completed the treatment period for study drug and achieved disease control (until confirmed progression of disease) and patients who have discontinued study drug due to toxicity or a reason other than confirmed progression of disease**

| Evaluation | Time Since Last Dose of Study Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months Thereafter (±2 weeks)[d] |
| | 30 | 2 | 3 | 4 | 6 | 8 | 10 | |
| Tumour assessment (CT or MRI)[c] | For patients who **achieve disease control following 12 months of treatment,** tumour assessments should be performed every 12 weeks relative to the date of **randomisation** until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 1 for timings of confirmatory scans.<br>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 for the first 48 weeks (per Table 1), then every 12 weeks thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 1 for timings of confirmatory scans.<br>Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional). | | | | | | | |

[a] World Health Organization 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 Organization performance status when information on subsequent anticancer therapy is provided, where possible.
[b] Coagulation tests: prothrombin time, APTT and INR will be performed if clinically indicated.
[c] 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. Following the final DCO for the study, patients continuing on the study who remain potentially eligible for future durvalumab re-treatment should receive tumour assessment scans and other assessments as per local clinical practice, but in such way that will allow confirmation of re-treatment eligibility criteria per Section 4.3. See Table 11 for tumour assessments done following approval of CSP Amendment 7.
[d] Patients on survival follow-up at the time of final DCO for the study will be considered to have completed the study and will continue to receive treatment per local standard of care.

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ADA Anti-drug antibody; AE Adverse event; APTT Activated partial thromboplastin time; BP Blood pressure; CT Computed tomography; INR International normalised ratio; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; PD Progression of disease; 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.

**Table 3 Schedule of study procedures: follow-up for patients who have discontinued study drug due to confirmed progression of disease**

| Evaluation | Time Since Last Dose of Study Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 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) and the health resource use | For patients who **continue on study drug post confirmed progression** at the Investigator's discretion (following consultation with the sponsor), patient questionnaires and information related to health resource use should be completed relative to the date of **randomisation** per Table 1 until study drug is stopped.<br>For patients who **discontinue study drug following confirmed progression**, patient questionnaires and information related to health resource use should be completed at the Day 30 assessment only. | | | | | | | |
| Physical examination | X | | | | | | | |
| Vital signs (BP, pulse, respiratory rate, temperature, oxygen saturation; see Section 6.4.8) | X | | | | | | | |
| Weight | X | | | | | | | |
| AE/SAE assessment | X | X | X | | | | | |
| Concomitant medications | X | X | X | | | | | |
| World Health Organization performance status[a] | X | X[a] | X[a] | X[a] | X[a] | X[a] | X[a] | X[a] |
| Subsequent anticancer 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 | X | | | | | |
| Serum chemistry | X | X | X | | | | | |
| Amylase, lipase (where available) | X | X | X | | | | | |
| Thyroid function tests (TSH, and T3 and T4) | X | | | | | | | |
| Coagulation parameters[b] | As clinically indicated → | | | | | | | |

**Table 3 Schedule of study procedures: follow-up for patients who have discontinued study drug due to confirmed progression of disease**

| Evaluation | Time Since Last Dose of Study Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 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 → | | | | | | | |
| Pharmacokinetic assessment | | | X | | | | | |
| Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) | | | X | | | | | |
| sPD-L1 concentration (to assess target engagement) | | | X | | | | | |
| Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) | X | | | | | | | |
| miRNA/mRNA (to examine immune cell gene expression profiles in circulation) | X | | | | | | | |
| Tumour biopsy (optional) | An optional tumour biopsy upon evidence of PD should be performed according to institutional practice. It is accepted that any biopsy procedure should be technically feasible and not associated with unacceptable clinical risk (see Section 6.7) | | | | | | | |
| Time to second progression[c] | 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 1 until study drug is stopped.<br>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. | | | | | | | |

**Table 3 Schedule of study procedures: follow-up for patients who have discontinued study drug due to confirmed progression of disease**

| Evaluation | Time Since Last Dose of Study Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months Thereafter (±2 weeks) |
| | 30 | 2 | 3 | 4 | 6 | 8 | 10 | |
| Tumour assessment (CT or MRI)[c] | 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 1 until study drug is stopped.<br>For patients who **discontinue study drug following confirmed progression**, **scans should be conducted according to local clinical practice** and submitted for central review until a new treatment is started (these scans are optional). | | | | | | | |

[a] World Health Organization 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 Organization 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] Study drug should be discontinued if there is confirmed progression of disease (PD) following a previous response (PR or CR) to study drug.
ADA Anti-drug antibody; AE Adverse event; APTT Activated partial thromboplastin time; BP Blood pressure; CT Computed tomography; INR International normalised ratio; miRNA Micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; PD Progression of disease; SAE Serious adverse event; sPD-L1 Soluble programmed death ligand 1; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

## 3.2 Rationale for study design, doses and control groups

### 3.2.1 Unmet need and potential role of immunotherapies in NSCLC

For patients with unresectable Stage IIIA or Stage IIIB disease combined modality therapy (chemoradiation) is superior to radiation alone and cCTRT is superior to sequential therapy (NCCN Guidelines 2014). Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide or cisplatin/vinblastine. For non-squamous NSCLC other cCTRT regimens include cisplatin/pemetrexed (NCCN Guidelines 2014).

However, the majority of patients inevitably progress (PFS is usually short; approximately 8 months) and 5-year OS is approximately 15% (Butts et al 2014). There is still therefore a significant unmet medical need for additional treatment options for use in this patient population to improve on OS and PFS (see Section 1.1.1).

Whilst advances have been made in improving survival from Stage III NSCLC by optimising local control, evidence suggests that cCTRT does not reduce the risk of distant relapse. With fewer cycles and, in some cases, lower doses of chemotherapy delivered in the concurrent setting, several studies have assessed whether delivering induction or consolidation treatment will improve survival. A pooled analysis of 41 Phase II/III trials confirmed that there remains no evidence to suggest that consolidation chemotherapy after cCTRT improves survival for patients with Stage III NSCLC and current guidelines continue to recommend cCTRT alone for the treatment of inoperable Stage III NSCLC (Bayman et al 2014). Given the lack of persuasive evidence for an active comparator, the use of a placebo comparator is justified in the proposed sequential/consolidation setting in this study.

The sequential/consolidation setting post-cCTRT may be ideal to evaluate the efficacy of immunotherapy, which is aimed at boosting the ability of the patient immune system to eliminate cancer cells. Chemoradiotherapy often induces initial tumour shrinkage followed by eventual PD as the tumours find mechanisms to bypass the chemoradiotherapy-induced growth inhibition. The initial tumour shrinkage observed in some patients following chemoradiotherapy is the result of cell death and tumour damage. Chemoradiotherapy-induced cell death can enhance the ability of the immune system to recognise and respond to the tumour through enhanced antigen release and presentation which, in turn, aids in the priming of immune cells to recognise and eliminate tumour cells. Therefore, triggering or augmenting an antigenic antitumour response with chemoradiotherapy and combining or following this treatment with anti-PD-L1 therapy, which acts to preserve ongoing immune responses by blocking an immunosuppressive signal theoretically may result in enhanced antitumour activity by improving local control and decreasing systemic spread.

### 3.2.2 Potential role for MEDI4736 in the treatment of NSCLC

Currently available data from the MEDI4736 FTIH study (Section 1.1.5 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, along with non-clinical and clinical data around combining an immune-modulator with chemotherapy and radiotherapy support the proposed investigation of sequential MEDI4736 in a controlled Phase III setting following cCTRT in patients with unresectable Stage IIIA or IIIB NSCLC. Updated safety and efficacy data from this FTIH study (CD ON MEDI4736 1108) was presented at international oncology conferences (Rizvi et al 2015).

### 3.2.3 Study design rationale

#### 3.2.3.1 Timing of treatment with MEDI4736 relative to concurrent chemoradiation therapy

Non-clinical data shows that both chemotherapy and ionising radiation up-regulate PD-L1 expression (Deng et al 2014, Zhang et al 2008b). In addition chemotherapy and radiotherapy both release new antigens leaving the cancer to act as an in situ vaccine that can elicit tumour-specific T-cells. Thus, starting MEDI4736 as close as possible to the completion of the cCTRT when antigen release and PD-L1 expression is most likely to be at its maximum will hopefully result in the most optimal benefit.

#### 3.2.3.2 Dose justification

Based on an analysis of the dose-escalation data from the ongoing FTIH study, a dose of 10 mg/kg Q2W administered for up to a maximum of 12 months is recommended for further development. This dosing regimen is expected to provide a level of PD-L1 inhibition that is predicted to result in a high probability of clinical response in the majority of patients.

This recommendation is supported by multiple lines of evidence including: in-vitro data, nonclinical activity, clinical PK-PDx, clinical biomarkers, and clinical activity data collected from the FTIH study. Based on the FTIH data, MEDI4736 exhibited non-linear (dose-dependent) PK consistent with target mediated drug disposition. A dose-dependent decrease in peripheral soluble PD-L1 was observed over the dose range of 0.1 to 10 mg/kg Q2W; consistent with engagement of MEDI4736 with PD-L1. Significant soluble PD-L1 (>90%) suppression at trough was observed with doses ≥0.3 mg/kg Q2W. PK parameters such as dose-normalised area under the drug concentration-time curve and $t_{½}$ increased over the dose range of 0.1 to 10 mg/kg Q2W and approached linearity at 3 mg/kg Q2W; suggesting near complete target saturation (membrane bound and soluble PD-L1) with 3 mg/kg Q2W. The expected mean trough concentration following 3 mg/kg Q2W MEDI4736 is ~50 µg/mL. Although clinical activity has been observed at lower doses, and DLTs have not been observed at the highest dose studied (10 mg/kg Q2W), this dose/schedule is anticipated to maintain levels above a target median trough concentration (100 µg/mL). The target trough serum concentration of 100 µg/mL accounts for the variability in PK (~50%), PDx response and clinical activity (up to 100%) anticipated in a diverse cancer patient population and to maintain sufficient PK exposure in case of an ADA impact. The target serum concentration of

100 µg/mL can be maintained with the 10 mg/kg Q2W dosing regimen. 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. Screening for ADA has detected 4 positive samples from 3 patients out of a total of 86 samples from 19 patients, with evidence for an impact on PK and target suppression in 1 individual. 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.

#### 3.2.3.3 Predictive biomarkers and rationale for an unselected population in Study D4191C00001

For this study, we propose not to restrict enrolment to any biomarker defined sub-population but where possible to carefully assess these patient characteristics in the context of this study, and other studies.

Tumour biopsies and viable tissue may be difficult to obtain post cCTRT. Tumours evolve with time and in response to treatment, and PD-L1 expression is likely to be different, post-cCTRT. In addition, non-clinical data shows that both chemotherapy and ionising radiation up-regulate PD-L1 expression (Deng et al 2014, Zhang et al 2008b). Therefore, PD-L1 expression from a biopsy sample prior to cCTRT may not accurately reflect the state of disease at the time the patient enrols in this study and is randomised to either MEDI4736 or placebo. In addition, tumours that are poorly immunogenic or that have become immunosuppressive can likely be made immunogenic through administration of pro-immunogenic therapies designed to increase antigen release from the cancer cell. Therefore, as stated, we propose not to restrict inclusion in this study based on PD-L1 expression from any tissue samples available. If it is feasible, biopsies will be taken post-CTRT and upon disease progression after randomisation to MEDI4736 or placebo. If possible based on the number and viability of the samples collected we will retrospectively assess whether there is any correlation between PD-L1 expression and response to treatment.

Current experience with single-agent immunotherapy studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. At the time of the initial writing of this protocol, no assay has been established/validated and no single approach has proven accurate for Stage 3 NSCLC patient enrichment for immune-mediated therapies. 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 for MPDL3280A at the American Society of Clinical Oncology (ASCO) conference 2013 (Powderly et al 2013) suggests 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 PD-L1-positive patients with 50% of patients who were PD-L1-positive

having SD and 33% having a PR. In contrast, in PD-L1 negative patients, they found only a 13% ORR with 28% of patients having SD and 13% having a PR. Importantly, a significant portion of patients (17%) that were negative for PD-L1 were able to respond to MPDL3280A treatment.

Similarly, in data presented at ASCO 2013 by Bristol-Myers Squibb (Grosso et al 2013) PD-L1 staining assessed using a different method and scoring algorithm appeared to be associated with greater clinical benefit in patients treated with nivolumab (anti-PD-1). They found a 44% ORR in PD-L1-positive patients versus a 17% ORR in PD-L1-negative patients. Additionally, in their studies, PD-L1-positive patients had a higher PFS (9.1 months versus 2.0 months) and OS than PD-L1 negative (21 months versus 12 months).

Therefore, while it appears that PD-L1 expression may improve the probability and/or quality of response to PD-1 pathway targeting agents and therefore, may have merit as an enrichment tool, it is important to note that the published findings are from single-arm trials and may not permit us to distinguish between prognostic factors or predictive markers for response to PD-L1 and PD-L1 therapies.

In conclusion, in this study biopsies immediately prior to randomisation to MEDI4736 or placebo and post-cCTRT will be difficult to obtain, in addition, biopsy material obtained prior to cCTRT may not accurately reflect PD-L1 status post-cCTRT as non-clinical data shows that both radiation and chemotherapy up-regulate PD-L1 expression. Therefore, we propose not to restrict enrolment to any biomarker defined sub population.

#### 3.2.3.4 **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) compared with placebo in terms of OS and PFS. 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). In certain settings, the utility of survival as an endpoint may potentially be confounded by subsequent therapies. Specifically, there are currently a number of molecules, targeting the PD-1/PD-L1 pathway, in late-stage development in second- and third-line squamous NSCLC. It is anticipated that these agents may be approved or become available for use through expanded-access mechanisms or additional clinical studies while this study is ongoing. This poses challenges in being able to fully characterize effects on OS if patients subsequently receive these immunotherapeutic agents. However, given that tumour response to immunotherapy may differ from typical responses, both PFS and OS are co-primary endpoints with the study powered for OS.

Antitumour activity will be assessed according to RECIST v1.1 guidelines, with the understanding that in the context of post-radiation changes tumour assessment may be difficult and may need to be repeated over time to reach a clear determination regarding responses and/progressive disease (see Section 6.3). The co-primary analysis of PFS will be based on programmatically derived PFS based upon BICR assessments. Sensitivity analyses will also be performed using data from site Investigators tumour data from all scans based

upon RECIST 1.1 and site Investigator tumour data from all scans based upon RECIST 1.1 modified for confirmation of progression. Exploratory analysis will also be performed for data obtained from the BICR on a subset of 250 evaluable patients scans using irRC.

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

1. Response to immunotherapy may be delayed

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

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

To account for these differences, RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Administration of study drug will continue between the initial assessment of progression and confirmation for progression.

In addition, patients may continue to receive study drug beyond confirmed PD in the absence of clinically significant deterioration and if Investigators consider that patients continue to receive benefit from treatment. Modification of RECIST as described may discourage the early discontinuation of study drug and provide a more complete evaluation of its antitumour activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumour progression that necessitates treatment with anti-cancer therapy other than MEDI4736 or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression).

#### 3.2.3.5 **Rationale for study endpoints (other exploratory endpoints)**

Biological samples will be used to explore potential biomarkers in tumour, plasma and/or serum, which may influence the progression of cancer (and associated clinical characteristics) and/or response.

Blood samples will be taken to allow for future exploratory research into genes/genetic factors that may influence response of MEDI4736 and/or agents used in combination and/or as comparators (PGx optional [DNA element]).

The assessment of health economic resource use data and derivation of health state utility will provide important information for payers and will be used within economic evaluations of MEDI4736.

#### 3.2.3.6 **Rationale for re-treatment beyond 12 months**

Justification for re-treatment beyond 12 months of MEDI4736:

- Targeted therapies have significantly increased both the rate and durability of response in patients with biomarker-enriched subsets of cancers including advanced NSCLC (eg, gefitinib and erlotinib in EGFR mutation positive, and crizotinib in ALK translocation positive) as well as in metastatic or unresectable melanoma (vemurafenib and dabrafenib in BRAF V600E mutation, trametinib in both V600E and V600K) (Maemondo et al 2010, Mok et al 2009, Mitsudomi et al 2010, Rosell et al 2011, Shaw et al 2013). Nevertheless, responses are mostly partial, and relapses are inevitable once resistance mechanisms emerge. Furthermore, the potential for tumour "addiction" and rapid clinical deterioration at the time of withdrawal and/or progression has been described (Asami et al 2013, Yoshimura et al 2013, Kim et al 2011, Yang et al 2013, Rizos et al 2014).

- In contrast to targeted therapy, responses have been observed upon re-treatment with immune-mediated therapy. Responses with immune-mediated therapy are no different than responses to initial treatment in terms of time to response, duration of response, or maintenance of response beyond treatment discontinuation (Hodi et al 2010, Forde et al 2014).

Therefore, patients who achieve and maintain disease control (ie, CR, PR or SD) through to the end of the 12-month study drug treatment period may also re-start treatment with study drug upon evidence of disease progression during follow-up.

The patient must not have received an intervening systemic anti-cancer therapy after discontinuing study drug and should have a baseline tumour assessment within 28 days of re-starting treatment with study drug (see Table 11).

# 4. PATIENT SELECTION CRITERIA

The patient population should be selected without bias.

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

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

## 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 histologically- or cytologically-documented NSCLC who present with locally advanced, unresectable (Stage III) disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology]), AND

4. Patients must have received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy, which must be completed within 1 to 42 days prior to first dose of investigational product in the study. For patients who are recovering from toxicities associated with prior treatment, first dose of investigational product may be delayed by up to 42 days from the end of the chemoradiation therapy.

   Sites are strongly encouraged to complete screening within the first 14 days of the 42-day screening period.

- The platinum-based chemotherapy regimen must contain one of the following agents: etoposide, vinblastine, vinorelbine, a taxane (paclitaxel or docetaxel), or pemetrexed, according to the local standard of care regimens.

- The final chemotherapy cycle must end prior to, or concurrently with, the final dose of radiation. Consolidation chemotherapy after radiation is not permitted but administration of chemotherapy prior to concurrent chemoradiation is acceptable.

- Where possible, chemotherapy regimens should be given according to National Comprehensive Cancer Network (NCCN) Guidelines or European Society for Medical Oncology (ESMO) Guidelines.

- Patients must have received a total dose of radiation of 60 Gy ±10% (54 Gy to 66 Gy) to be randomised as part of the chemoradiation therapy. Sites are encouraged to adhere to mean organ radiation dosing as follows:
  - Mean lung dose must be <20 Gy and/or V20 must be <35%
  - Mean eosophagus dose must be <34 Gy
  - Heart V45 <35% or V30 <30%.
- Sites should be aware of the recent RTOG 0617 Trial data demonstrating that doses higher than 60 Gy may be associated with greater toxicity and worse efficacy.

5. Patients must have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

6. Tumour sample requirements:

- 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)
- A recent (≤3 months) tumour biopsy (taken following completion of the most recent therapy) is an optional requirement, provided that a biopsy procedure is technically feasible and the procedure is not associated with unacceptable clinical risk

7. Life expectancy ≥12 weeks at Day 1

8. World Health Organization (WHO) Performance Status of 0 or 1

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

- Women <50 years old would be considered post-menopausal 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 post-menopausal 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).

10. Adequate organ and marrow function as defined below:

- Absolute neutrophil count >1.5 x $10^9$/L (1500 per $mm^3$)
- Platelets >100 x $10^9$/L (100,000 per $mm^3$)
- Haemoglobin ≥9.0 g/dL (5.59 mmol/L)
- Serum creatinine 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:

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

Females:

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

- 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.
- AST and ALT ≤2.5 x ULN.

**Genetics research study (optional)**

For inclusion in the optional (DNA) genetics research study patients must fulfil the following criteria:

- Provide informed consent for the genetic sampling and analyses.

If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

## 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

or

- Prior randomisation or treatment in a previous durvalumab (MEDI4736) and/or tremelimumab clinical study regardless of treatment arm assignment

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 who receive sequential chemoradiation therapy for locally advanced NSCLC.

7. Patients with locally advanced NSCLC who have progressed whilst definitive platinum based, concurrent chemoradiation therapy.

8. Receipt of any immunotherapy, or investigational drug within 4 weeks prior to the first dose of study drug; and in the case of monoclonal antibodies 6 weeks prior to the first dose of study drug.

9. Current or prior use of immunosuppressive medication within 28 days before the first dose of study drug, 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. Systemic steroid administration required as prophylaxis against or to manage toxicities arising from chemotherapy and/or radiotherapy delivered as part of the chemoradiation therapy for locally advanced NSCLC is allowed.

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

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

12. Patients with ≥grade 2 pneumonitis from prior chemoradiation therapy.

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

14. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment.

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 drug.

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 any excipient.

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

22. 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.

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

24. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study drug.

25. History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

- Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer in situ.

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.

27. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the study drug or interpretation of patient safety or study results.

**Genetics research study (optional)**

Exclusion criteria for participation in the optional (DNA) genetics research component of the study:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients are provided in Section 5.3.

## 4.3 Criteria for treatment through progression of disease and re-treatment

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 study drug.

For all patients who completed the first 12-month period of treatment with study drug and had CR, PR or SD at completion, re-treatment 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, or 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 re-treatment or treatment through progression informed consent (criterion 1). These consent documents will specify that treatment beyond initial evidence of PD or re-treatment 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 10) and the criterion for AST/ALT.

The patient should not enter re-treatment 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 or prior use of immunosuppressive medication within 28 days before the first dose of study drug, 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 previously receiving study treatment, or any unresolved irAE >Grade 1 (criterion 13)
- 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 14)
- Recent major surgery within 4 weeks prior to dosing (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)
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction (criterion 21)

- 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 22)

- Active infection of tuberculosis, as determined by clinical signs and symptoms (criterion 23)

- Receipt of live attenuated vaccination within 30 days prior to dosing or within 30 days of receiving study drug (criterion 24)

- 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 26)

- 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 27).

At the time of the final DCO for the primary analyses of PFS and OS, study patients randomised to the durvalumab arm who have not progressed and who meet the above eligibility criteria will remain in the study. At the time the patient progresses, and re-treatment with durvalumab is felt to be their best treatment option, then at the time of re-treatment they must meet the above eligibility criteria. Patients' eligibility should be recorded in their medical records. Re-treatment will not be available within this protocol following the final DCO for the long-term follow-up phase of the study (CSP amendment 7).

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).

# 5. STUDY CONDUCT

## 5.1 Restrictions during the study

1. 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 after the final dose of study drug; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

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

   – Patients must use 2 acceptable methods of effective contraception as described in Table 4.

2. Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 4) from Day 1 and for 90 days after receipt of the final dose of study drug.

**Table 4 Effective methods of contraception (two 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. Patients should not donate blood whilst participating in this study.

Restrictions relating to concomitant medications are described in Section 5.6.

## 5.2 Patient enrolment and randomisation

At Visit 1 (Screening), the Principal Investigator, or suitably trained delegate, will:

1. Obtain signed informed consent (main study) from the potential patient before any study specific procedures are performed. Procedures that are part of standard of care may occur before informed consent is obtained.

2. Assign 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) (ECCNN08X: CC being the country code. NN being the centre number, 08X 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 patient eligibility. See Sections 4.1 and 4.2.

At Visit 2 (Randomisation/Baseline), once the patient is confirmed to be eligible, the Principal Investigator, or suitably trained delegate, will:

4. Call IVRS/IWRS to assign the eligible patient a unique randomisation code (patient number). Randomisation codes will start at 001 and 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.

### 5.2.1 Procedures for randomisation

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

At Visit 2, patients who satisfy all the entry criteria will be centrally assigned to study drug by the IVRS/IWRS, according to the randomisation scheme generated by the Biostatistics Group, AstraZeneca, or delegate.

Patients will be randomised in a 2:1 ratio to either MEDI4736 (10 mg/kg) or placebo. Patients will be stratified at randomisation based on their: age at randomisation (<65 years versus ≥65 years of age), sex (male versus female), and smoking history (smoker versus non-smoker).

The actual study drug given to patients will be determined by the randomisation scheme in the IVRS/IWRS. The randomisation scheme will be produced by a computer software program called GRand (AstraZeneca Global Randomisation system) that incorporates a standard procedure for generating randomisation numbers. One randomisation list will be produced for each of the randomisation strata. 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 unblinded 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 study drug. It is recommended that patients commence study drug as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS system).

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 study drug 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 for the study. 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 drug

**Patients who fail to meet the inclusion/exclusion criteria** should not, under any circumstances, be enrolled or receive study medication. 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 study drug, or where patients subsequently fail to meet the study criteria post initiation, a discussion must occur between the IQVIA' Physician and the Investigator regarding the patient's safety and well-being and whether to continue or discontinue the patient from study drug.

The IQVIA Physician is to ensure all such contacts are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study drug 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 PFS and OS where possible.

## 5.4 Blinding and procedures for unblinding the study

### 5.4.1 Methods for ensuring blinding

The study will be conducted in a double-blind manner. The reconstituted MEDI4736 solution and its matching placebo will be identical in colour and the iv bags used for administration will be identical with regards to size. All study drug will be blinded using an opaque sleeve, fastened with tamper-evident tape over the iv bag prior to dispensing to other study personnel to maintain the double-blind conditions.

The patient, the Investigator and study centre staff will be blinded to study drug allocation. The study centre pharmacist will be unblinded to study drug and will prepare MEDI4736 or placebo for a patient as specified by the randomisation scheme and IVRS (only the unblinded pharmacist will know the randomisation/treatment allocation details). Pharmacists will be given specific instructions for study drug preparation and will note if the double-blind conditions have been compromised or the blind broken. Lot numbers of MEDI4736 dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. Other study centre staff and monitors will not be given access to lot number information.

No member of the extended study team at AstraZeneca/MedImmune, at the investigational centres, or any Contract Research Organisation handling data will have access to the randomisation scheme 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 drug, the drug safety departments at AstraZeneca/MedImmune, and pharmacists required to dispense the study drug at the study site. Investigators will only be unblinded to treatment allocation in cases of medical emergency.

The treatment codes and results will be kept strictly within AstraZeneca/MedImmune to safeguard the integrity of the blind, and hence to minimize any possible bias in data handling.

The IDMC will be provided with unblinded data for their review but AstraZeneca/MedImmune and IQVIA staff and Investigators involved in the study will remain blinded.

### 5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists at the study centre from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca/MedImmune, without revealing the treatment given to a patient to the AstraZeneca/MedImmune staff. There is no known antidote to MEDI4736, and IQVIA/the Medical Monitor should be contacted with any

concerns. Hence, overdose will not normally be considered a reason for breaking the blind. If the treatment code is broken then the Investigator(s) must document and report to AstraZeneca/MedImmune.

AstraZeneca/MedImmune retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. 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. If the blind is broken, the date, time and reason will be recorded in IVRS, and any associated AE report. If a patient's study drug is unblinded by the Investigator, or designee, the patient will be withdrawn from study drug as described in Section 5.8.

For the BICR, blinded data will be provided.

## 5.5 Treatments

### 5.5.1 Identity of investigational product(s)

The Investigational Products Supply section of AstraZeneca/MedImmune will supply MEDI4736 to the Investigator as a lyophilised powder for reconstitution. The saline solution for the matching placebo will be sourced locally.

| Investigational product | Dosage form and strength | Manufacturer |
|---|---|---|
| MEDI4736 | Supplied as a lyophilised powder containing 200 mg MEDI4736. When reconstituted with 4.0 mL of water for injection, the solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, 0.02% (weight/volume) polysorbate 80, at pH 6.0 | AstraZeneca/MedImmune |
| Placebo | Matching placebo for injection; saline solution | To be sourced locally |

#### 5.5.1.1 Product preparation of MEDI4736

The dose of investigational product for administration must be prepared by the Investigator's or site's designated investigational product manager using aseptic technique. Commercially available water for injection and 0.9% (weight/volume) saline will be supplied by each site. Total in-use storage time from reconstitution of MEDI4736 to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36 to 46°F). If the in-use storage time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives and any unused portion must be discarded.

**Reconstitution of investigational product**

MEDI4736 requires reconstitution prior to use. The reconstitution should be performed with 4.0 mL sterile water for injection for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted MEDI4736 should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

**Preparation of MEDI4736 doses for administration with an iv bag**

Doses of 10 mg/kg will be administered using an iv bag containing 0.9% (weight/volume) saline, with a final MEDI4736 concentration ranging from 1 to 20 mg/ml, and delivered through an iv administration set with a 0.2-µm or 0.22-µm in-line filter.

Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. An additional volume of 0.9% (weight/volume) saline equal to the calculated volume of MEDI4736 to be added to the iv bag must be removed from the bag prior to addition of MEDI4736. The calculated volume of MEDI4736 is then added to the iv bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

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

**Dose calculation**

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

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

Example: For a patient weighing 80 kg, dosed at 10 mg/kg, 16 mL [10 mg/kg × 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in an iv bag containing 0.9% (weight/volume) saline. First, 16 mL of saline is removed from the iv bag, and then 16 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.

### 5.5.2 Doses and treatment regimens

Patients enrolled in the study will receive either MEDI4736 10 mg/kg or placebo via iv infusion Q2W ±3 days. Administration of study drug will commence on Day 1 following randomisation to MEDI4736 or placebo after confirmation of eligibility and will continue on a Q2W schedule for a maximum duration of 12 months (see Table 1). Study drug should be discontinued prior to 12 months if there is confirmed PD (unless the Investigator considers the patient continues to receive benefit from study drug), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue study drug occur.

Disease progression requires confirmation. In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study drug until progression has been confirmed.

If progression is not confirmed, then the patient should continue on study drug and on treatment assessments.

Patients who achieve and maintain disease control (CR, PR, NED or SD) through to the end of the 12-month treatment period will enter follow-up per Table 2. 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 study drug for as long as the Investigator judges that they are gaining clinical benefit with the same treatment guidelines followed during the initial 12-month treatment period (Table 1). Patients will only be able to restart study drug 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 study drug, and cannot continue to receive study drug will enter follow-up with assessments as shown in Table 3.

Patients with confirmed PD that 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 in the initial treatment period but for as long as the Investigator judges that they are gaining clinical benefit in the re-treatment period (and will follow the assessments in Table 1 including tumour assessments).

Study drug should be discontinued if there is confirmed progression of disease (PD) following a previous response (PR or CR) to study drug.

For all patients who receive study drug through disease progression and patients who achieve disease control and restart study drug 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 meet the inclusion and exclusion criteria specified in Section 4.3. The patient 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 study drug.

#### 5.5.2.1 Study drug administration

Following preparation of MEDI4736 (see Section 5.5.1.1) or matched placebo, the entire contents of the iv bag should be administered as an iv infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm 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), is not known, the 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 study drug administration must be recorded in the source documents.

**Monitoring of dose administration**

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

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to 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.

### 5.5.3 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 study drug 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).

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-mediated adverse event (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab 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

Following the first infusion of study drug, subsequent administration of study drug can be modified based on toxicities observed as described in the TMGs. All toxicities will be graded according to CTCAE Version 4.03.

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

Dose modifications will not be required for AEs that are clearly not attributed to 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.

#### 5.5.3.1 MEDI4736 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. Unless they meet SAE criteria, AESIs will not be recorded during the Extension Study.

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 AESI 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 include:

- Diarrhoea / 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).

**Pneumonitis**

Pneumonitis has been reported in association with use of anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). It is also seen in 5% to 15% of patients irradiated for breast, lung, and mediastinal tumours. The risk of developing radiation pneumonitis is directly related to the volume of irradiated lung, the amount of radiation given, and the use of concurrent chemotherapy. Additional risk factors include co-morbid lung disease, poor baseline pulmonary function testing, and low performance status.

**Radiation pneumonitis**

Symptoms of radiation pneumonitis, including low-grade fever, congestion, dry cough, pleuritic chest pain, and a sensation of chest fullness, usually develop 1 to 3 months after completion of radiation therapy. Diagnosis is difficult, often complicated by co-morbid conditions and radiation injury to adjacent structures (eg, oesophagus, pericardium). Prednisone, in dosages of at least 50 to 60 mg per day for 1 week followed by an extended taper, has been shown to abate symptoms and improve lung function. Bronchodilators and supplemental oxygen may be necessary.

More specific guidelines for the evaluation and treatment of pneumonitis are described in detail in the TMGs.

### 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 (GMP) and local regulatory guidelines. The labels will fulfil GMP 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 drug dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study code
- Enrolment code
- Directions for use
- The name of the Principal Investigator, where applicable (this may be pre-printed or added on the label when the study drug is dispensed)
- The period of use eg, expiry date.
- Product Lot Identifier
- Medication Identity Number
- For clinical study use only.

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 investigational product label on the kit specifies the appropriate storage. MEDI4736 must be stored at 2°C to 8°C.

## 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 anticancer 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).
- 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. Use of immunosuppressive medications in patients for the management of study drug-related AEs or their use in patients with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.
- Live attenuated vaccines within 30 days of dosing. Inactivated viruses such as those in the influenza vaccine are permitted.

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 medication 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 durvalumab as re-treatment following the final DCO for the study will be recorded in site documents for the purpose of supply management but will not otherwise be reported.

Use of investigational product 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.

### 5.7.1 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 investigational product

Patients may be discontinued from investigational product 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 one or more of the exclusion criteria for study participation at study entry and continuing study drug might constitute a safety risk
- Any AE that meets criteria for discontinuation, as defined in Section 5.5.3
- An AE related to study drug that is ≥Grade 3, with the exception of toxicities that do not meet criteria for discontinuation as defined Section 5.5.3
- ≥Grade 3 infusion reaction
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment
- Pregnancy or intent to become pregnant.

If the patient is discontinued from study drug, 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 for the study, SAEs occurring in patients on treatment or in the 90 day follow up period after the last dose of durvalumab must be reported directly to AstraZeneca

Global Patient Safety as described in Section 6.4.4. Other AEs should be managed according to the durvalumab TMGs (refer to Section 5.5.3), and will be followed up per the Investigators' judgment but will not otherwise be reported or recorded for the purposes of this study. Following the final DCO for the study, Investigators who intend to commence or continue re-treatment with durvalumab 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 investigational product

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

A patient that decides to discontinue investigational product 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 returned by the patient.

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

**Assessments following withdrawal of study drug**

Patients who are permanently discontinued from receiving study drug will remain in the study and will be followed per the study plans in Table 2 or Table 3 including the collection of any protocol-specified blood specimens and completion of questionnaires and case report forms (CRFs) 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 for the study, at which time, unless they remain eligible for re-treatment with durvalumab, they will be considered to have completed the study. Re-treatment will not be an available treatment option within this protocol following the final DCO for the long-term follow up phase of the study (CSP amendment 7). 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 (Table 2 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]). 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 on-going 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 drug must be recorded in the eCRF and reported as SAEs, if applicable.

Patients who have disease control following completion of 12 months of treatment or patients who are withdrawn from study drug for reasons other than confirmed PD will continue to have objective tumour assessments (see Table 2).

Drug or study procedure related SAEs must be captured until the patient completes the follow-up period following discontinuation of study drug (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 Table 3 (for patients discontinuing due to confirmed PD) (by telephone contact with the patient, patient's family, or by contact with the patient's current physician. An exception is any patient with confirmed PD that continues to receive study drug at the discretion of the Investigator (following consultation with the sponsor), who can receive study drug for a maximum of 12 months during the initial treatment period or for as long as the Investigator judges that they are gaining clinical benefit in the re-treatment period and will follow the assessments in Table 1 including tumour assessments until study drug 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 progression of disease (PD) following a previous response (PR or CR) to study drug.

Both the patient and the physician will be asked about the subsequent treatment the patient receives during the follow-up period (Table 2 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]).

## 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 (investigational product 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 Sections 6.4.3 and 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 drug 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 (Table 2 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]). 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

The schedule for assessments at Screening and during the Treatment Period is presented in Table 1. The schedule of study procedures during follow-up for patients who have completed study drug and achieved disease control (until confirmed PD) and patients who have discontinued study drug due to toxicity or a reason other than confirmed PD is presented in Table 2. The schedule of study procedures during follow-up for patients who have discontinued study drug due to confirmed PD is presented in Table 3. Following final DCO for the study, 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 durvalumab (ie, re-treatment patients) or is in the 90-day safety follow-up period after receiving the last dose of durvalumab. Investigators with patients in progression 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. From the date CSP amendment 7 is implemented, assessment schedule in Table 11 is to be followed.

## 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 42 days prior to the first infusion of study drug (Table 1). For details of the nature of the assessments, see below.

- Signed informed consent for the study and assignment of a patient identification number
- Verify eligibility criteria
- Demographic details including age, sex and ethnicity and also tobacco and alcohol consumption history
- Past medical and surgical history (including previous treatments for NSCLC)

- Physical examination to assess all conditions that are current and ongoing
- Weight, height and vital signs: systolic blood pressure (BP) and diastolic BP, pulse, respiratory rate, body temperature and oxygen saturation
- Recording of AEs from the time of 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, 5 level health state utility index [EQ-5D-5L])
- Mandatory provision of an unstained, archived tumour tissue sample in a quantity sufficient to allow for analysis. Please refer to the Laboratory Manual for details.
- A recent tumour biopsy (taken following completion of the most recent therapy) is an optional requirement, provided that a biopsy procedure is technically feasible and the procedure is not associated with unacceptable clinical risk. See Section 6.7.
- Blood samples for the analysis of biomarkers (including those for circulating soluble factors, and messenger RNA/micro RNA, and soluble PD-L1). See Section 6.7.
- A sample for PGx (DNA) analysis (optional)

- Tumour assessment scans of the chest and abdomen (including liver and adrenal glands) for assessment of disease by CT/MRI (see Appendix F).

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 drug if any discontinuation criteria are fulfilled, see Section 5.8. The assessments to be carried out during follow-up are detailed in Table 2 (for patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (for patients discontinuing due to confirmed PD).

Any serious and/or non-serious AEs ongoing at the time of study drug 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.

#### 6.2.2.1 Survival follow-up

Assessments for survival status should be made following confirmed objective disease progression (per RECIST v1.1 criteria) as presented in Table 2 (for patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (patients discontinuing due to confirmed PD). 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 durvalumab. Survival follow-up for all patients will end within this protocol with the completion of the long-term follow up part of the study (CSP amendment 7).

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, which will take place approximately 62 months from the start of randomisation, 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 confirmed 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

For both BICR and Investigator review, 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, NED, SD or PD) are presented in Appendix F. Localised post-radiation changes which affect lesion sizes may occur and there may be high levels of necrosis/fibrosis with little or no active tumour in recently irradiated lesions. However, accepting these limitations in this patient population with prior curative radiation treatment the prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

The methods 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. Additional anatomy should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up.

The baseline assessment is part of the screening procedures and should be performed within 0 to 42 days after the end of chemoradiation therapy and before the start of study drug. For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks for the first 12 months (relative to the date of randomisation; Table 1), then every 12 weeks thereafter (Table 2) until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping study drug 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.

Patients who achieve and maintain disease control (ie, CR, PR, NED, or SD) through to the end of the 12-month treatment period may restart treatment with study drug upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up. To restart study drug the patient must not have received an intervening systemic anti-cancer therapy post-study drug discontinuation. Patients who restart study drug must have a baseline tumour assessment within 28 days of restarting study drug, all further scans should occur every 8 weeks (relative to the date of restarting study drug). If a patient is continuing to receive

re-treatment after final DCO for the study or continuing in progression-free follow-up, they should receive scans/RECIST and other assessments per the local standard of care.

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 (relative to the date of randomisation) then every 12 weeks thereafter until confirmed objective disease progression.

Disease progression requires confirmation, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. A biopsy (optional biopsy at suspected progression) may assist with the differentiation of malignant tumour from post-radiation changes and may be of assistance at the Investigator sit in confirming the malignant origin of regrowth within the radiation field. However, confirmatory radiological assessments should still be performed at the next schedule visit to confirm radiological progression. Administration of study drug will continue between the initial assessment of progression and confirmation for progression. For all patients who are treated through progression and patients who achieve disease control and restart study drug 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 re-treatment 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.

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 study drug until progression is confirmed.

If progression is not confirmed, then the patient should continue study drug and on treatment assessments.

If a patient discontinues study drug (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. Patients with no evidence of disease at follow-up in the absence of new lesions will be assigned a response of NED. 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 study drug.

If there is doubt as to whether progression has occurred, particularly with non-target lesion or the appearance of a new lesion, it is advisable to continue study drug 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 one 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 plan (Table 3). An exception is patients with confirmed PD that continue to receive study drug at the discretion of the Investigator (following consultation with the sponsor); these patients can receive study drug for a maximum of 12 months and will have scans every 8 weeks (relative to the date of randomisation per Table 1) until study drug is stopped.

Study drug should be discontinued if there is confirmed progression of disease (PD) following a previous response (PR or CR) to study drug.

Patients with confirmed PD that discontinue study drug, should have scans conducted according to local standard clinical practice (see Section 6.2.2.2) and submitted for BICR until the patient commences a new treatment (these scans are optional; see Table 3).

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans (Table 1 [Screening and the Treatment Period], Table 2 [for follow-up of patients

achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]) and Appendix F.

### 6.3.1 Central reading of scans

The co-primary analysis for this study will be based on PFS from BICR using assessment of tumours using RECIST 1.1. In addition, an exploratory analysis of PFS from BICR by assessment of tumours using irRECIST 1.1 (Wolchok et al 2009, Nishino et al 2013) will be conducted (see Section 12.2.3 for the analysis methods). All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation for central analysis. Results of these independent reviews will not be communicated to Investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the Investigator.

## 6.4 Safety

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

Safety guidelines around SAE reporting described within the protocol remain in effect after the final DCO for the study.

### 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, run-in, treatment, washout, follow-up), that fulfils one 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 informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of study drug). Adverse events not meeting SAE criteria that occur after the final DCO for the study in patients still on durvalumab will be followed up as per standard clinical practice but will not be recorded for the purposes of this study.

SAEs will be recorded from the time of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of study drug).

After the final DCO for the study, any SAEs occurring whilst the patient is either still receiving durvalumab (ie, re-treatment patients) or is in the 90-day safety follow-up period after receiving the last dose of durvalumab must be reported to AstraZeneca following the procedures outlined in Section 6.4.4. If a patient discontinues from study drug 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 informed consent until the patient is withdrawn from 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 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 safety follow-up period. 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 the investigational product, 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
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- 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 investigational product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

A guide to the interpretation of the causality question is found in Appendix 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 nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of study drug) 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 with the investigational product. 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.

**NB.** Cases where a patient shows an AST **or** ALT ≥3 x ULN **or** total bilirubin ≥2 x 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 x ULN, one or more also show elevation of serum total bilirubin to >2 x 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 drug 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 drug, 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 receiving study drug or 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 the investigational product, or to the study procedure(s). All SAEs occurring prior to final DCO for the study 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, IQVIA) immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca/MedImmune representative (ie, IQVIA) 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 IQVIA 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.

After the final DCO for the study, any SAEs occurring whilst the patient is either still receiving durvalumab (ie, re-treatment patients) or in the 90 day safety follow up period after receiving the last dose of durvalumab are to be recorded in the 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 Table 1 (Screening and the Treatment Period), Table 2 (follow-up for patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (follow-up for patients discontinuing due to confirmed PD). 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. Patients receiving re-treatment after final DCO for the study are to undergo sampling for laboratory assessments in such a way that continued per-protocol re-treatment eligibility can be properly determined. 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 durvalumab in order to manage AEs in accordance with the durvalumab TMGs (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 5, Table 6 and Table 7.

**Table 5 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 6 Clinical chemistry (serum or plasma)**

| | |
|---|---|
| Albumin | Glucose |
| Alkaline phosphatase[a] | Lactate dehydrogenase |
| Alanine aminotransferase[a] | Lipase[b] |
| Aspartate aminotransferase[a] | Magnesium[b] |
| Amylase[b] | Potassium |
| Bicarbonate | Sodium |

**Table 6 Clinical chemistry (serum or plasma)**

| | |
|---|---|
| Albumin | Glucose |
| Calcium | Total bilirubin[a] |
| Chloride | Total protein |
| Creatinine (creatinine clearance)[b] | Urea or blood urea nitrogen, depending on local practice |
| Gamma glutamyltransferase[c] | Uric acid[b] |

[a] Tests for aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin must be conducted concurrently and assessed concurrently.
[b] 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.
[c] Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated. Clinical chemistry assessments to be performed at each visit and when clinically indicated.

**NB.** In case a patient shows an AST **or** ALT ≥3 x ULN **or** total bilirubin ≥2 x 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 drug should have a further liver chemistry profile (AST, ALT, bilirubin and alkaline phosphatase) performed 30 days (±7days) after permanent discontinuation of study drug.

**Table 7 Urinalysis**

| | |
|---|---|
| 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 at Screening, Day 1, every 4 weeks of 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 Common Toxicity Criteria (CTC) Grade 3 or 4 laboratory values at the time of completion or discontinuation from study drug 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 schedules (Table 1 [Screening and the Treatment Period], Table 2 [for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]). Patients receiving re-treatment after final DCO for the study 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 Table 1, Table 2, and Table 3 based on the following:

1. Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia

2. 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.

3. Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours

4. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

5. 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 World Health Organization performance status when information on subsequent anticancer therapy is provided, where possible.

### 6.4.7 Electrocardiogram

Clinical interpretation and management of patients for all ECGs will be done locally.

The same method of assessment should be used throughout.

Electrocardiograms will be recorded at 25 mm/sec.

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been rested in a supine position for at least 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTc value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding. Patients receiving re-treatment after final DCO for the study 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.

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/√R) must be <470 msec.

### 6.4.8 Vital signs

For timings of assessments refer to the study plans in Table 1 (Screening and the Treatment Period), Table 2 (for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD). Patients receiving re-treatment after final DCO for the study 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 will be monitored with assessment of vital signs (BP, 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.

#### 6.4.8.1 Pulse and blood pressure

Blood pressure and pulse will be collected 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 BP and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

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 1. 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 only performed at Screening and if 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 (TSH and T3 free [if available] and total T4 [or T4 free]) are shown in Table 1 (Screening and the Treatment Period), Table 2 (for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD).

## 6.5 Patient reported outcomes

Timings of the assessments for PRO are presented in Table 1 (Screening and the Treatment Period), Table 2 (for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD). 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 whereas higher scores indicate greater functioning, greater QoL, or greater level of symptoms (Aaronson et al 1993). The EORTC QLQ C30 questionnaire should be completed before the LC13 module.

### 6.5.2 Lung Cancer Module (LC13)

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, 5-level health state utility index (EQ-5D-5L)

The EuroQoL 5-dimension utility index (EQ-5D) 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).

Since 2009, the EuroQol group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L) which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability and an improved ability to differentiate between different levels of health (Janssen et al 2008a, Janssen et al 2008b, Pickard et al 2007).

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

The assessment of health state utility will provide important information for payers and will be used within economic evaluations of MEDI4736.

### 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 (Table 1 [on-treatment], Table 2 and Table 3 [follow-up]).

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.

## 6.6 Pharmacokinetics and ADA

### 6.6.1 Collection of PK samples and determination of drug concentration

Blood samples (3.5 mL) for determination of MEDI4736 in serum will be taken at the times presented in the study plans in Table 1 (Screening and the Treatment Period), Table 2 (for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD). Patients receiving re-treatment after final DCO for the study will not undergo drug concentration or anti-drug antibody assessments.

Measurement of MEDI4736 concentrations in serum will be performed using a validated immunoassay. Samples for determination of MEDI4736 concentrations in serum will be analysed by a designated third party on behalf of AstraZeneca/MedImmune, using an electrochemiluminescence assay. The lower limit of quantification of MEDI4736 in serum is 50 ng/mL; however, this is dependent on the assay used.

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 taken according to the schedule presented in Table 1 (Screening and the Treatment Period), Table 2 (for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (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

Mandatory tumour and blood biomarkers to be evaluated to support the exploratory objectives of the study are described in Section 6.7.1 through Section 6.7.4. Alternative biomarkers may be evaluated as determined by additional data associated with disease progression or response to MEDI4736.

Biomarker assessments that may have the potential to identify patients likely to respond to treatment with MEDI4736 (determined from other MEDI4736 studies) will be investigated to determine a patient's biomarker status and for possible correlation with efficacy endpoints.

Exploratory biomarker research, beyond the scope of the secondary endpoint assessments, will not form part of the CSR. The results may be pooled with biomarker data from other MEDI4736 studies to test existing hypotheses or to generate hypotheses to be tested in future studies of NSCLC and MEDI4736.

Samples will be taken at the times presented in the study plans in Table 1 (Screening and the Treatment Period), Table 2 (for follow-up of patients achieving disease control or who are discontinued due to toxicity or a reason other than confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD). For blood volume see Section 7.1. Patients receiving re-treatment after final DCO for the study will not undergo biomarker analyses.

### 6.7.1 Collection of patient selection biomarker data

At Screening, an unstained, archived tumour tissue sample (formalin fixed paraffin embedded [FFPE]) in a quantity sufficient to allow for analysis (see the Laboratory Manual) must be deemed to be available. If an archived tumour block cannot be shipped for this study, then at least 10 newly cut, unstained slides with tissue sections of 4 microns thick may be provided for analysis as described in the Laboratory Manual.

An optional image-guided core needle (at least 18 gauge) tumour biopsy following completion of the most recent therapy, or upon evidence of PD after randomisation to MEDI4736 or placebo, should be performed according to institutional practice, provided it is not associated with unacceptable clinical risk. If provided, the sample should be of a sufficient quantity to allow for analysis (see the Laboratory Manual). Tumour lesions planned for biopsy must not be used as index lesions for assessment of disease.

If tumour biopsies are taken and it is clinically practical, patients will undergo 4 core biopsies, but a minimum of at least 3 core biopsies are required. The first and third core biopsies will be placed in formalin and processed for FFPE, while the second and fourth core biopsies (fourth biopsy, if available) will be immediately frozen in liquid nitrogen and then stored at -80°C (where such storage facilities exist).

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.

The expression and spatial distribution of PD-L1 protein within the tumour microenvironment will be evaluated for any relationship with efficacy endpoints.

### 6.7.2 Blood borne biomarkers

Blood or tissue samples will be analysed to evaluate protein, nucleic acid, and cellular biomarkers that relate to MEDI4736 treatment.

Blood and tissue collected for analysis of immune cell gene expression profiles within the peripheral and tumoural compartments will be evaluated for any relationship with efficacy endpoints.

Blood (plasma or serum) samples will also be collected for analysis of circulating soluble factors in relation to immune status at baseline and in response to treatment. Factors to be analysed may include but are not limited to: the presence of IFN-γ tumour necrosis factor-α, interleukin (IL)-2, IL-6, IL-10, IL-8, IL-12, and levels of soluble PD-L1, as well as antibodies against tumour, self, or viral antigens.

### 6.7.3 Tumour samples (immune-related or response-related markers)

The expression and spatial distribution of immune-related or response-related markers by immunohistochemistry may also include, but may not be limited to, PD-L1, CTLA-4, CD3, CD4, CD8, CD45RO, forkhead box P3, granzyme B, OX40, PD1, cleaved caspase 3 and Ki67. Archived material (or biopsies if available), may also be analysed for the presence of key mutations which may include but are not limited to: *EGFR, K-ras, N-ras, B-raf, anaplastic lymphoma kinase* and the met proto oncogene to evaluate their potential relevance and correlations with response to MEDI4736 treatment.

### 6.7.4 Genomic analysis

Whole blood and tumour samples will be collected for RNA and/or micro RNA/messenger RNA sample preparation. Ribonucleic acid may be used in the analyses of transcript and/or micro RNA expression and stored for future analyses. Ribonucleic acid analyses will be conducted to evaluate its utility to identify subsets of patients responsive to MEDI4736.

### 6.7.5 Management of biomarker data

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

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

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

## 6.8 Pharmacogenetics

### 6.8.1 Collection of pharmacogenetic samples

Refer to Appendix D for details of the genetic research (optional DNA component). For blood volume see Section 7.1.

## 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 drug. Table 8 is 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 follow-up or during re-treatment following the final DCO for the study are to be in accordance with the Investigator's judgment and local institutional practice.

Laboratory assessments should be monitored in such a way that continued per-protocol re-treatment eligibility can be properly determined. It is recommended that Investigators

monitor the patient's safety laboratory assessments prior to and periodically during the treatment with durvalumab in order to manage AEs in accordance with the durvalumab TMGs (refer to Section 5.5.3).

**Table 8 Volume of blood to be drawn from each patient 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 | 7 | **7.0** |
| | Coagulation | 3.0 | 1 | **3.0** |
| Pharmacokinetic(s) | | 3.5 | 3 | **10.5** |
| Biomarkers | Soluble PD-L1(to assess target engagement) | 3.5 | 2 | **7.0** |
| | ADA testing including ADA neutralising antibodies (to identify ADA responses in patient circulation) | 8.5 (1 x 3.5 mL sample and 1 x 5.0 mL sample) | 2 | **17.0** |
| | Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) | 5.0 | 3 | **15.0** |
| | miRNA/mRNA (to examine immune cell gene expression profiles in circulation) | 5.0 mL sample at Randomisation 2.5 mL at other timepoints | 2 | **7.5** |
| Pharmacogenetic(s) | | 8.5 | 1 | **8.5** |
| **Total** | | **44 mL** | **38** | **102.5 mL** |

ADA Anti-drug antibody; 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

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research will be retained at AstraZeneca/MedImmune R&D or an appropriate vendor selected by AstraZeneca/MedImmune, on behalf of AstraZeneca/MedImmune for a maximum of 15 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the CSR but separately in a Scientific Publication.

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 disposed of after the CSR has been finalised. 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. Samples will be stored for a maximum of 15 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

Refer to Appendix D for details of the optional (DNA) genetic research.

## 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.

IQVIA 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.

All data protection and confidentiality principles are applicable to the biomarker research.

## 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 Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the 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.

For all patients who are treated through progression and patients who achieve disease control and restart study drug upon evidence of confirmed 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 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 study drug.

Patients who are eligible for re-treatment following final DCO for the study must sign the re-treatment informed consent prior to receiving durvalumab. 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

IQVIA is responsible for the management of this study and thus throughout this section IQVIA 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.

### 9.3.1 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.

### 9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

## 9.5 Study timetable and end of study

If the study reaches statistical significance for PFS/OS at the interim or final analyses, additional follow-up for that particular endpoint may occur based on the needs for long term follow up with more mature data in order to estimate the long-term benefit for MEDI4736. The study will continue until all analyses for long term PFS/OS benefit are complete and those patients who have been in OS and PFS follow-up for approximately 5 years will be considered to have completed the study. Patients who have been progression free for approximately 5 years are considered cured and will no longer be considered eligible for retreatment within this protocol. Those patients who are still actively in retreatment, and continuing to receive clinical benefit, will have the option to continue on study drug on an alternate rollover or extension protocol.

The roll-over or safety extension study will 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 may be terminated at individual centres once there are no longer any patients being treated or followed in progression-free or overall survival follow up or once the final DCO for the study has occurred and all queries at that centre have been resolved.

### 9.5.1 Data collection after the primary analysis of PFS and OS

If the study achieves statistical significance for the co-primary endpoints of PFS and/or OS at one of the planned interim analyses, then that will be considered the final analysis for that endpoint. Further analyses for that particular endpoint may still occur depending on the need to have long-term follow up or more mature data; the last DCO of the study will then be the last assessment of long-term benefit.

Patients who are receiving MEDI4736 due to re-treatment after both primary analyses of PFS and OS have been conducted may continue receiving MEDI4736 treatment, if the Investigator judges that they are gaining clinical benefit. It is recommended that the patients continue the scheduled site visits and that Investigators monitor the patient's safety laboratory results prior to and periodically during the treatment with MEDI4736 in order to manage AEs in accordance with the MEDI4736 TMGs (refer to Section 5.5.3). A summary of study procedures to be followed for patients in long-term follow up or in re-treatment (effective at the time of approval of CSP Amendment 7) is presented in Table 11.

Patients in progression-free follow up will receive tumour assessment scans in accordance with Table 11 (effective at the time of approval of CSP Amendment 7) up to the time of final DCO and 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. Scans are to be submitted for BICR in the same manner that they were during the treatment portion of the study.

Patients in progression-free follow up and who are eligible for re-treatment (ie, patients who were randomised to the MEDI4736 arm, who completed the initial 12 months of treatment,

and who meet the eligibility criteria for re-treatment [see below]) remain eligible for possible future re treatment upon progression for up to ~5 years following their initial study randomisation if they still meet the re-treatment eligibility criteria and the Investigator judges that the patient will gain clinical benefit at that time. Patients who progress >3 years after randomisation must have a biopsy to confirm that this is a true recurrence of their original tumour and not a new primary lesion to allow for confirmation of their eligibility for re-treatment.

Eligibility criteria for re-treatment:

- The patient must provide signed, written and dated consent through the re-treatment informed consent form (criterion 1). This consent document will specify re-treatment 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.
- A biopsy is mandated at the time of progression if more than 3 years have passed since randomisation as confirmation of true recurrence of the original tumour and not a new primary lesion; the Investigator must consult with the Study Physician if such sampling is not feasible.
- The patient must 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 10) and the criterion for AST/ALT.

<u>The patient should not enter re-treatment if any of the following exclusion criteria are fulfilled:</u>

- 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 or prior use of immunosuppressive medication within 28 days before the first dose of study drug, 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 previously receiving study treatment, or any unresolved irAE >Grade 1 (criterion 13)
- 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 14)

- Recent major surgery within 4 weeks prior to dosing (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)
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction (criterion 21)
- 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 22)
- Active infection of tuberculosis, as determined by clinical signs and symptoms (criterion 23)
- Receipt of live attenuated vaccination within 30 days prior to dosing or within 30 days of receiving study drug (criterion 24)
- 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 26)
- 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 27).

Data collection during long-term follow up:

After the primary analysis of PFS and OS is conducted, all data will be recorded on patient charts only, and not in the WBDC system, with the exception of the following which will continue to be collected and recorded on the WBDC system (see Table 9):

**Table 9 eCRFs to be completed during long-term follow up**

| Assessment to be captured | Relevant CRF page to be completed |
|---|---|
| RECIST assessments: tumour assessments should be performed relative to the date of randomisation as follows: every 26 weeks (±4 weeks) until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 11 for timings of confirmatory scans. | RECIST1TLF, RECIST1NTLF, RECIST2NL, RECISTVR |
| Survival : every 8 weeks (±1 week) | SURVIVE |
| Statement of death | DEATH |
| Subsequent anti-cancer therapy | CAPRXPOST, CAPRXRPOST, CONPRO |
| Hospitalisations and hospital resource utilisation | HOSPAD |
| Specific concomitant medications for all patients regardless of treatment arm and disease status (supportive care therapy – see Table 10) | MED |
| All SAEs experienced by patients whilst receiving treatment with MEDI4736 or within 90 days of discontinuing MEDI4736 must continue to be reported to the Sponsor within the usual timelines (ie, immediately, or no later than 24 hours of when the site becomes aware of the SAE; see Section 6.4.4). If a SAE is reported then all data relevant to the SAE (eg, concomitant medications, laboratory data, dosing data, new medical or surgical history) should be submitted as part of the SAE report | SAE |

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 monotherapy are provided in the TMGs. The most current version of these guidelines is to be maintained within the Site Master File. In addition, a version of the current TMGs is available through the following link:

https://tmg.azirae.com

Please contact the Clinical Research Associate for information on how to gain access to this website.

Review of patient charts may be conducted periodically as needed by AstraZeneca or an authorised representative.

**Table 10 Concomitant medications/Supportive Care therapy of interest during safety follow up**

| | |
|---|---|
| 1 | Pain medications |
| 2 | Antibiotics (systemic) |
| 3 | Antifungals (systemic) |
| 4 | Antiemetics |
| 5 | Red blood cell transfusion |
| 6 | Platelet transfusion |
| 7 | Erythropoiesis-stimulating agents (ESAs) |
| 8 | Granulocyte-colony stimulating factor (GCSF) |
| 9 | Steroids (Dosing and duration of treatment are particularly important) |
| 10 | Anti-depressants |

## Table 11 Schedule of study procedures: Long-term follow-up and re-treatment period after primary PFS and OS analyses

| Assessment[a] | Frequency |
|---|---|
| **Patients in survival follow-up** | |
| Survival assessment | Q8w (±1w) |
| Hospital resource utilisation | As applicable but at least Q12w |
| Concomitant medications (see section 9.5.1 & Table 10) | As applicable but at least Q12w |
| Subsequent anti-cancer therapy | As applicable |
| **Patients in progression-free follow-up** | |
| Survival assessment | Q8w (±1w) |
| Hospital resource utilisation | As applicable but at least Q12w |
| Concomitant medications (see section 9.5.1 & Table 10) | As applicable but at least Q12w |
| Tumour assessment (CT or MRI) | Q26w (±4w)[c] |
| **Patients eligible for or receiving re-treatment up to ≤90 days post last dose** | |
| Written informed consent for re-treatment only (Note: Patients are required to re-consent to continue study drug when restarting study drug following initial disease control [See Section 8.4]) | Upon determination of progression. |
| Verification of eligibility criteria for re-treatment (including tumour biopsy[d]) | Upon determination of progression. |
| Survival assessment | Q8w (±1w) |
| Hospital resource utilisation | As applicable, but at least Q12w |
| MEDI4736 (Durvalumab) administration for re-treatment[b] | Q2w (±3d) |
| Serious adverse event assessment (see sections 6.4.2, 6.4.3 and 6.4.4) | As applicable |
| Concomitant medications (see section 9.5.1 & Table 10) | As applicable, but at least Q12w |
| Tumour assessment (CT or MRI) | Q26w (±4w) [c] |
| Vital signs, haematology, serum chemistry[a] | It is recommended that for re-treatment patients haematology, clinical chemistry, thyroid function and vital signs continue to be assessed as per the initial 12 month treatment period as detailed in Table 1. |

[a] Assessments are to be performed at the times stipulated and as clinically required in the management of the patient. 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 durvalumab as per the schedule of study procedures above in order to manage AEs in accordance with the durvalumab toxicity management guidelines (refer to

Section 5.5.3). It is recommended that results for urea and electrolytes, full blood count and liver function tests should be available before commencing an infusion. If screening laboratory assessments are performed within 3 days prior to Day 1, they do not need to be repeated at Day 1. All assessments to be performed pre-infusion unless stated otherwise.

[b] Patients with confirmed PD who continue to receive study drug at the discretion of the Investigator (following consultation with the sponsor) can receive study drug for as long as the Investigator judges that 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. Study drug should be discontinued if there is confirmed progression of disease (PD) following a previous response (PR or CR) to study drug.

[c] Q26w (±4w) relative to date of randomisation until confirmed PD by RECIST 1.1 by investigational site review. An additional scan should be performed following any scan indicating progression and submitted for BICR review.

[d] The collection of tumour biopsies at the time of progression prior to re-treatment is mandated if more than 3 years have passed since randomisation; the Investigator must consult with the Study Physician if such sampling is not feasible.

CT Computed tomography; MRI Magnetic resonance imaging; PD Progression of disease.

### 9.5.2 Data collection after the final DCO for the study

The last DCO of the study will be the last assessment of long-term benefit. After the final DCO, patients in OS and PFS follow-up will be considered to have completed the study. Patients who are receiving treatment at time of final DCO may continue receiving investigational product if the Investigator judges that they are gaining clinical benefit.

For re-treatment patients who do continue to receive study drug beyond the time of the final DCO, Investigators will report SAEs to AstraZeneca/Medimmune Patient Safety until 90 days after study drug is discontinued, 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 TMGs (refer to 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 for the study, SAE reporting applies only to patients who are still receiving MEDI4736 or who are in the 90-day safety follow up period post the last dose.

## 10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by IQVIA.

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 WHO Drug Dictionary. All coding will be performed by IQVIA.

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.

## 11.1 Calculation or derivation of efficacy variable(s)

### 11.1.1 RECIST 1.1 based endpoints

#### 11.1.1.1 Blinded Independent Central Review of RECIST 1.1-based assessments

The BICR of all radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be provided to the BICR. Prior radiotherapy reports will also be provided to the BICR to allow the selection of appropriate target lesions. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD or not evaluable [NE]) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD). Endpoints (of PFS, ORR, and DoR) will be derived from the overall visit response date and the scan dates.

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

#### 11.1.1.2 Investigator RECIST 1.1-based assessments

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study drug or receives another anti-cancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, NED, SD, or PD depending on the status of their disease compared with baseline and previous BICR assessments. Patients with no evidence of disease at follow-up in the absence of new lesions will be assigned a response of NED. The baseline assessment is part of the screening procedures and should be performed within 0 to 42 days after the end of chemoradiation therapy and before the start of study drug. For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 42 days from the end of the chemoradiation therapy.

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

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

### 11.1.2 Blinded Independent Central Review of irRC-based assessments

The definitions of CR, PR, SD and PD according to irRECIST 1.1, as outlined by Wolchok et al 2009, Nishino et al 2013, will be outlined clearly in the Imaging Charter.

### 11.1.3 Co-primary endpoints

The co-primary endpoints are OS and PFS.

#### 11.1.3.1 Overall survival

OS 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. Death dates may be found by checking publicly available death registries.

#### 11.1.3.2 Progression free survival

PFS (per RECIST 1.1 as assessed by the BICR) 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 prior to the 2 missed visits. 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 scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of either reviewer where both select PD as a time point response and there is no adjudication for central review (BICR) data

- For investigational assessments, 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 in the RECIST eCRF 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.

Additionally, PFS will be obtained using the algorithm described above for the RECIST BICR data, but following a modification whereby any objective disease progression must be confirmed by the next scheduled scan. The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression. If disease progression is confirmed (or disease progression occurs and no further scans are recorded) then the date of progression will be when it was originally observed. Patients with a single disease progression and no further tumour assessment scans will be treated as PD in the analysis.

In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study drug until progression has been confirmed.

For exploratory purposes, PFS will also be obtained using the irRC data obtained from BICR. Objective disease progressions also require confirmation under this approach.

### 11.1.4 Proportion of patients alive at 24 months

The proportion of patients alive at 24 months (ie, OS24) will be defined as the Kaplan-Meier estimate of OS at 24 months.

### 11.1.5 Objective response rate

ORR (per RECIST 1.1 as assessed by BICR) is defined as the number (%) of patients with at least 1 visit response of CR or PR and will be based on all randomised patients who have measurable disease. If the BICR finds any patients do not have measurable disease at baseline then the analysis of ORR for the BICR data will exclude these patients, so that the denominator is a subset of the Intent-to-Treat (ITT) population who have measurable disease at baseline per BICR. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy and then respond will not be included as responders in the ORR.

ORR will also be obtained using the algorithm described above for the RECIST site Investigator tumour data. The denominator is a subset of the Intent-to-Treat (ITT) population who have measurable disease at baseline per the site Investigator.

Additionally, ORR will be obtained using the algorithm described above from the RECIST BICR data, but following a modification where any objective progression requires confirmation. Therefore, data obtained up until confirmed progression, or the last evaluable assessment in the absence of a confirmed progression, will be included in the assessment of ORR. Note that the response may be after an unconfirmed progression.

For exploratory purposes, ORR will also be obtained for the irRC data obtained from BICR.

### 11.1.6 Duration of response

DoR (per RECIST 1.1 as assessed by BICR) 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 (Section 11.1.3.2).

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. Only patients with measurable or non-measurable disease at baseline can achieve an objective response of CR and only patients with measurable disease at baseline can achieve an objective response of PR.

If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time.

DoR will not be defined for those patients who do not have documented response.

### 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 at 12 months.

### 11.1.8 Proportion of patients alive and progression free at 18 months

The proportion of patients alive and progression free at 18 months (ie, APF18) will be defined as the Kaplan-Meier estimate of PFS at 18 months.

### 11.1.9 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 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.

### 11.1.10 Time to death or distant metastasis

TTDM will be defined as the time from the date of randomisation until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST 1.1 or proven by biopsy. Patients who have not developed distant metastasis 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 has distant metastasis or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. 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.

## 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 study drug will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 90 days of discontinuation of investigational product (ie, the last dose of MEDI4736 or placebo) may be included in the AE summaries, but the majority of those summaries will omit those AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study drug) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of study drug 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 drug.

The QT interval corrected for heart rate using Fridericia's formula (QTcF) will be derived during creation of the reporting database using the reported ECG values (RR and QT).

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

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

Corrected calcium (mmol/L) = Total Calcium (mmol/L) + ([40 – Albumin (G/L)] x 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.

#### 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 (Osoba et al 1998). 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 12.

**Table 12 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 drug or receives another anticancer 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 drug or receives another anticancer 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) 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 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 of >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 of ≤90.

#### 11.3.1.2 LC13

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 improvement, no change or deterioration as shown in Table 13.

**Table 13 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 drug or receives another anticancer 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 of >10.

#### 11.3.1.3 Calculation or derivation of health state utility (EQ-5D-5L)

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). A unique EQ-5D health state is referred to by a 5 digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where value sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied (Oemar and Janseen 2013). In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

## 11.4 Calculation or derivation of pharmacokinetic variables

### 11.4.1 PK non-compartmental analysis

The actual sampling times will be used in the PK calculations. MEDI4736 concentration data and summary statistics will be tabulated. Individual and mean blood MEDI4736 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 and steady-state doses: peak concentration and trough concentration will be reported after the first or steady-state dose, 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 MEDI4736 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 antibodies. The immunogenicity titre and presence of neutralizing ADA will be reported for samples confirmed positive for the presence of anti-MEDI4736 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)

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

## 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

## 12.1 Description of analysis sets

A comprehensive SAP will be prepared. The Full Analysis Set (FAS) and the Safety Analysis Set described below will be applied to all randomised patients.

Table 14 gives a summary of outcome variables and analysis populations.

**Table 14 Summary of outcome variables and analysis populations**

| Outcome variable | Populations |
|---|---|
| **Efficacy Data** | |
| OS, PFS | ITT |
| OS24, ORR, DoR, APF12, APF18, PFS2, PRO endpoints, and TTDM | ITT |
| Demography | ITT |
| PK data | PK |
| **Safety Data** | |
| Exposure | Safety |
| Adverse events | Safety |
| Laboratory measurements | Safety |
| Vital Signs | Safety |

APF12 Proportion of patients alive and progression free at 12 months from randomisation; APF18 Proportion of patients alive and progression free at 18 months from randomisation; DoR Duration of response; ITT Intent-to-Treat; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomisation; PFS Progression free survival; PFS2 Time from randomisation to second progression; PK Pharmacokinetic; PRO Patient reported outcomes; TTDM Time to death or distant metastasis.

### 12.1.1 Full analysis set

**Intent-to-treat:** The primary statistical analysis of the efficacy of MEDI4736 versus placebo will include all randomised patients 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 drug are included in the ITT population. Note, this is also known as the FAS. 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 one dose of randomised study drug (MEDI4736 or placebo) and for whom any post-dose data are available 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 per the protocol, for whom any post-dose data are available and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set. The population will be defined by the Study Team Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

## 12.2 Methods of statistical analyses

There will be 1 treatment comparison of interest:

- MEDI4736 10 mg/kg versus placebo

OS and PFS are co-primary endpoints and the study has been sized to characterise the OS and PFS benefit of MEDI4736 10 mg/kg.

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 infusion of study drug, 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 ITT analysis set.

Safety data will be summarised on the safety analysis set.

Results of all statistical analysis will be presented using a 95% confidence interval (CI) and p-value, unless otherwise stated.

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

**Table 15 Formal statistical analyses to be conducted and pre-planned sensitivity analyses**

| Endpoints Analysed | Notes |
|---|---|
| Overall Survival | Primary analysis using a stratified log-rank test<br>Sensitivity analysis using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias |
| Progression Free Survival | Stratified log-rank test using BICR tumour data (RECIST 1.1)<br>Sensitivity analyses using BICR tumour data (RECIST 1.1)<br>1) Interval censored analysis – evaluation time bias<br>2) Analysis using alternative censoring rules – attrition bias<br>Sensitivity analysis stratified log-rank test using site Investigator tumour data (RECIST 1.1) – ascertainment bias<br>Sensitivity analysis stratified log-rank test using BICR tumour data (RECIST 1.1, modified for confirmation of progression) – confirmation bias<br>Exploratory analysis stratified log-rank test using BICR tumour data (irRC) |
| Proportion of patients alive at 24 months | Hazard ratio using the Kaplan-Meier estimates of survival at 24 months (following the method described by Klein et al 2007) |
| Objective Response Rate | Fisher's exact test using BICR tumour data (RECIST 1.1)<br>Sensitivity analysis using the Fisher's exact test using site Investigator tumour data (RECIST 1.1)<br>Sensitivity analysis using the Fisher's exact test using BICR tumour data (RECIST 1.1, modified for confirmation of progression)<br>Exploratory analysis using the Fisher's exact test using BICR tumour data (irRC) |
| Duration of Response | Analysis following the method described by Ellis et al 2008 using BICR tumour data (RECIST 1.1) |
| Proportion of patients alive and progression free at 12 and 18 months | Hazard ratio using the Kaplan Meier estimates of progression free survival at 12 and 18 months (following method described by Klein et al 2007) |
| Time from randomisation to second progression | Stratified log-rank test |
| Time to death or distant metastasis | Stratified log-rank test using site BICR tumour data (RECIST 1.1) |

**Table 15 Formal statistical analyses to be conducted and pre-planned sensitivity analyses**

| Endpoints Analysed | Notes |
|---|---|
| Symptom improvement rate (EORTC QLQ-C30 and LC13 endpoints) | Logistic regression |
| QoL/Function improvement rate (EORTC QLQ-C30 endpoints) | Logistic regression |
| Time to QoL/Function deterioration (EORTC QLQ-C30 endpoints) | Stratified log-rank test<br>Sensitivity analysis using alternative censoring rules – attrition bias |
| Time to symptom deterioration (EORTC QLQ-C30 and LC13 endpoints) | Stratified log-rank test<br>Sensitivity analysis using alternative censoring rules – attrition bias |
| Change from baseline (EQ-5D-5L health state utility values and Visual Analogue Scale) | Mixed model repeated measures analysis |

BICR Blinded Independent Central Review; 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; irRC Immune-related response criteria; LC13 Lung Cancer Module; QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumours.

All outputs will be summarised 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 OS24 and ORR.

There will be up to 4 DCO time points in the study. The DCO for the interim PFS analysis (first analysis) will be done when 367 PFS events have occurred (52% maturity), approximately 30 months after the first patient is randomised. The DCO for the primary PFS analysis (second analysis) and the first interim OS analysis will be done when at least 458 PFS events have occurred (65% maturity) at approximately 36 months after first patient is randomised (with approximately 285 OS events, 41% maturity). The third analysis DCO will occur at the time of the second OS interim analysis when it is expected that 393 OS events have occurred (56% maturity, approximately 47 months after the first patient is randomised). The DCO for the primary OS analysis (fourth analysis) will be done when 491 OS events have occurred (70% maturity) at approximately 62 months.

The overall 5% type 1 error will be split between the co-primary endpoints OS and PFS. An alpha level of 2.5% will be allocated to OS analysis and PFS analysis equally. An interim PFS analysis for superiority will occur when approximately 367 PFS events have occurred and

the primary PFS analysis will be performed when 458 PFS events have accumulated. The 2.5% alpha level allocated to PFS 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 significance level applied at the interim depends upon the proportion of information available. If 80% of the PFS events required at the time of the primary PFS analysis is available at the time of the interim (ie, 367/458 PFS events have occurred), the 2-sided significance level to be applied for the PFS interim analysis would be 1.04% and the 2-sided significance level to be applied for the primary PFS analysis would be 2.19%.

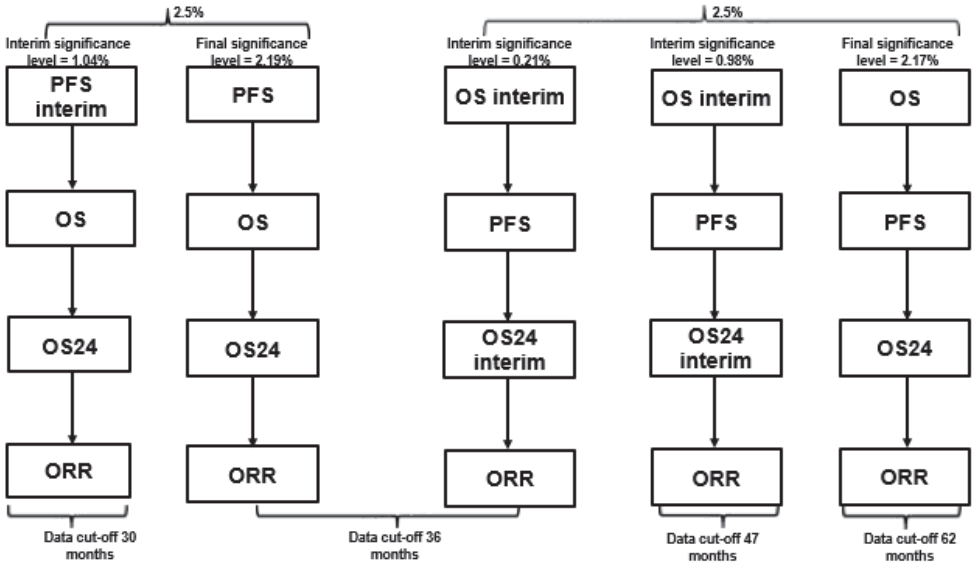
The first interim OS analysis for superiority will occur at the time of the primary PFS analysis and the second interim OS analysis will occur when it is expected that 393 OS events have occurred. The 2.5% alpha level allocated to OS will be controlled at the interim and primary time point by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the significance level applied at the interim depends upon the proportion of information available. For example, if 58% and 80% of OS events required at the time of the primary OS analysis is available at the time of the interim (ie, 285/491 and 393/491 events have occurred), the 2-sided significance level to be applied for the OS interim analysis would be 0.21% and 0.98% respectively, and the 2-sided significance level to be applied for the primary OS analysis would be 2.17%.

At the time of the primary PFS, interim OS and primary OS analyses, hypotheses will be tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses will be tested in a pre-defined order. 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 will then be tested in the multiple testing procedure using a weighted proportion of alpha (test mass; the total test mass equals alpha) and test mass that becomes available after each rejected hypothesis is recycled to the hypotheses not yet rejected. This testing procedure stops when the entire test mass is allocated to non-rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), amongst all key hypotheses.

At the primary PFS analysis, if significance is achieved on the primary PFS analysis, then the alpha will be recycled to OS primary analysis followed by the secondary endpoints, OS24 and ORR.

Similarly, if OS is significant at the interim analysis, the available alpha will be recycled to PFS primary analysis followed by the secondary endpoints. If OS is significant at the primary analysis timepoint, available alpha will be recycled to PFS primary analysis followed by the secondary endpoints. Spending alpha between secondary endpoints in this way will strongly control type I error (Glimm et al 2009). Figure 3 shows the multiple testing framework.

**Figure 3 Multiple testing procedures for controlling the type 1 error rate**




### 12.2.2 Co-primary endpoints

#### 12.2.2.1 Overall survival

The primary analysis of the co-primary endpoint, OS, will occur when approximately 491 deaths have occurred (approximately 70% maturity). OS will be analysed using a stratified log-rank test adjusting for age at randomisation (<65 versus ≥65 years of age), sex (male versus female), and smoking history (smoker versus non-smoker).

The effect of treatment will be estimated by the hazard ratio (HR) together with its corresponding 97.5% CI and p-value for the ITT population.

The HR and CI can be estimated from the stratified log-rank as follows (Berry et al 1991, Collett 2003, Selke and Siegmund 1983):

$$HR = \exp\left(\frac{U}{V}\right)$$

$$95\%\ \text{CI for HR} = \left(\exp\left\{\frac{U}{V} - \frac{1.96}{\sqrt{V}}\right\}, \exp\left\{\frac{U}{V} + \frac{1.96}{\sqrt{V}}\right\}\right)$$

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki}, -e_{1ki})$ $U = \sum_k U_k = \sum_k \sum_i (d_{1ki}, -e_{1ki})$ is the stratified log-rank test statistic obtained from the SAS LIFTEST procedure, $\sqrt{V} = \sqrt{\sum_k V_k}$ $\sqrt{V} = \sqrt{\sum_k V_k}$, is its standard deviation, k denotes the stratum and $d_{1ki}$ and $e_{1ki}$ are the observed and expected events in Group 1, stratum k.

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

The assumption of proportionality will be assessed. 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 is a result of treatment-by-covariate interactions, which will be investigated.

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

Subgroup analyses will be conducted comparing OS between treatments in the following subgroups of the FAS:

- Age at randomisation (<65 versus ≥65 years of age)
- Sex (male versus female)
- Smoking status (smoker versus non-smoker).

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. Before embarking on more detailed modelling, an initial model will be constructed, containing treatment and the stratification factors alone, to ensure any output from the Cox modelling is likely to be consistent with the results of the stratified log-rank test.

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985.

Additionally, for each subgroup, the HR (MEDI4736: placebo) and 95% CI will be calculated from a log-rank test within each individual subgroup. These will be presented on a forest plot including the HR and 95% CI from the overall population.

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.

#### 12.2.2.2 **Progression free survival**

The primary analysis of the co-primary endpoint, PFS, will occur when it is expected that 458 PFS events have occurred (65% maturity). PFS based upon the BICR data will be analysed using a stratified log-rank test adjusting for the same factors as for OS. The effect of treatment will be estimated by the HR together with its corresponding 97.5% CI and p-value for the full ITT population. Kaplan-Meier plots of PFS will be presented by treatment arm. 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 assumption of proportionality will be assessed in the same way as for OS. The analysis will be based on the programmatically derived PFS using BICR 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 timepoints. 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.

Ascertainment bias will be assessed by analysing site Investigator data. The stratified log-rank test will be repeated on the programmatically derived PFS using the site Investigator data based upon RECIST. The HR and CI will be presented.

If there is an important discrepancy between the primary analysis using the BICR and this sensitivity analysis using site Investigator data assessments, then the proportion of patients with site but no central confirmation of progression will be summarised; such patients have the potential to introduce bias in the central review due to informative censoring. An approach that imputes an event at the next visit in the central review analysis may help inform the most likely HR value (Fleischer et al 2011), but only if an important discrepancy exists.

An additional analysis using the BICR tumour data will be performed to determine the effect of confirmation of progression. The stratified log-rank test will be repeated on the programmatically derived PFS using BICR tumour data based upon RECIST modified for confirmation of progression. The HR and CI will be presented.

An exploratory analysis of PFS using the irRC data obtained from the BICR will be performed. The stratified log-rank test will be repeated on PFS using the BICR based upon the irRC data. The HR and CI will be presented.

Subgroup analyses and a forest plot will be provided comparing PFS between treatments in the same way as previously specified for OS. Unless there is a marked difference between the results of the statistical analyses of the PFS from the BICR tumour data and that of the site Investigator, this will only be performed upon the programmatically derived PFS endpoint using BICR data based upon RECIST.

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 Proportion of patients alive at 24 months (OS24)

The proportion of patients alive at 24 months (ie, OS24) will be summarised (using the Kaplan-Meier curve) and presented by treatment arm. It will be compared between treatments by using the Kaplan-Meier estimator of survival at 24 months for each treatment to obtain the HR. The HR and CI will be presented.

### 12.2.4 Objective response rate

The ORR will be based on the programmatically derived RECIST using the BICR data. The ORR will be compared between MEDI4736 versus placebo using a Fisher's exact test. A binary response variable for ORR will be used for the analysis with the categories of CR and PR versus SD, PD and NE. The results of the analysis will be presented in terms of the proportion of responders and a p-value.

This analysis of ORR will be repeated using the results of the programmatically derived PFS using the site Investigator data from all scans based upon RECIST as a sensitivity analysis to confirm the results of the primary analysis derived from the CRFs. An additional sensitivity analysis will be performed on ORR using BICR tumour data based upon RECIST modified for confirmation of progression to determine if there is any difference when using progression confirmation rules. Finally, an exploratory analysis of ORR using the irRC data obtained from the BICR will be performed where the above analysis will be repeated.

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, NED, SD, PD, NE). No formal statistical analyses are planned for BoR.

### 12.2.5 Duration of response

In order to analyse the DoR between arms the Expected Duration of Response (EDoR) will be derived for each treatment arm (Ellis et al 2008) for the BICR tumour data. The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients and provides an estimate based on all randomised patients. Treatments will be compared by calculating the ratio of EDoRs, using an appropriate probability distribution (to be specified in the SAP) for DoR in responding patients. Additionally, 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).

### 12.2.6 Proportion of patients alive and progression free at 12 months (APF12)

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.

### 12.2.7 Proportion of patients alive and progression free at 18 months (APF18)

The proportion of patients alive and progression free at 18 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 18 months for each treatment to obtain the HR. The HR and CI will be presented.

### 12.2.8 Time from randomisation to second progression (PFS2)

PFS2 will be analysed using identical methods as outlined for the analysis of PFS 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. The sensitivity analysis outlined in Section 12.2.2.2 will not be repeated for PFS2 with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of PFS2 is reversed.

### 12.2.9 Time to death or distant metastasis

TTDM will be analysed using identical methods as outlined for the analysis of PFS 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. The sensitivity analysis outlined in Section 12.2.2.2 will not be repeated for TTDM with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of TTDM is reversed.

### 12.2.10 Patient reported outcomes

The PRO endpoints that have been identified as primary are EORTC QLQ-C30 time to QoL deterioration of global health status and LC13 time to symptom deterioration for each of dyspnoea, cough, haemoptysis, and pain. These are not part of the main multiple testing procedure but 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.

#### 12.2.10.1 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 sensitivity analysis to ascertain attrition bias will be performed as described for the primary analysis of OS for those endpoints identified as primary. However, subgroup analyses and treatment interaction testing will not be performed. 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. The odds ratio and 95% CI for each scale/item will be presented graphically on a forest plot. If there are very few responses in one treatment arm, a Fisher's exact test will be considered.

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.

#### 12.2.10.2 **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 sensitivity analysis to ascertain attrition bias will be performed as described for the primary analysis of OS for those endpoints identified as primary. However, subgroup analyses and treatment interaction testing will not be performed. 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. The odds ratio and 95% CI for each symptom will be presented graphically on a forest plot. If there are very few responses in one treatment arm, a Fisher's exact test will be considered.

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.

#### 12.2.10.3 **EuroQol-5-Dimension 5-Level questionnaire**

The change from baseline in health state utility values and the visual analogue scale will be compared between treatment arms at each visit using a mixed model repeated measures analysis, which adjusts for the same factors as the primary analysis and also the baseline health state utility value/visual analogue scale as appropriate. Adjusted mean differences between treatments and 95% CIs from these analyses will be presented, but, as this analysis is exploratory in nature, p-values will not be calculated.

Descriptive statistics will be reported for the health state domain (eg, proportion in each domain) and the visual analogue scale by visit, as well as the change in the visual analogue scale value and the derived utility index value from baseline. To support future economic evaluations, additional appropriate analyses may be undertaken, for example, mean health state utility pre- and post-treatment, and pre- and post-progression.

### 12.2.11 Healthcare resource use

An exploratory health economic analysis of hospital episodes including type of contact (hospitalisation, outpatient, day case), reason, length of stay by ward type (including intensive care unit) and procedures and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of MEDI4736. This would include providing descriptive statistics as appropriate, including means, median and ranges.

### 12.2.12 Safety data

Safety and tolerability data will be presented by treatment arm 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 re-treatment with MEDI4736 will be produced separately.

Other safety data will be assessed in terms of physical examination, clinical chemistry, haematology, vital signs and ECGs. Exposure to MEDI4736 and placebo will be summarised. Time on study and MEDI4736/placebo dose interruptions will also be summarised. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

### 12.2.13 PK data

MEDI4736 concentration data will be listed for each patient and each dosing day, and a summary provided for all evaluable patients.

#### 12.2.13.1 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 antibodies. The immunogenicity titre and neutralising ADA data will be listed for samples confirmed positive for the presence of anti-MEDI4736 antibodies.

### 12.2.14 PK/PDx relationships

If the data are suitable, the relationship between MEDI4736 PK exposure and efficacy/safety parameters may be investigated graphically or using appropriate data modelling approach.

### 12.2.15 Biomarker data

The relationship of PD-L1 expression and if applicable, of exploratory biomarkers to OS, PFS, ORR and DoR will be presented for a subset of patients in the ITT population who are evaluable for each biomarker.

This will be assessed using similar summary and graphical representations to those that are outlined for the efficacy outputs in Section 12.2.2 to 12.2.5.

PD-L1 expression determined by immunohistochemistry will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

### 12.2.16 Interim analysis

Up to 3 interim analyses will be performed, one for PFS and two for OS. The DCO for the interim analysis of PFS will occur when it is expected that 367 PFS events have occurred (52% maturity, approximately 30 months after the first patient is randomised). The DCO for the first interim analysis of OS will occur when it is expected that 458 PFS events have occurred (65% maturity, approximately 36 months after the first patient is randomised). It is expected that approximately 285 death events (41% maturity) will be available for the interim OS analysis (assuming OS HR=0.73). The second interim analysis of OS (the third interim analysis) will be conducted when it is expected that 393 OS events have occurred (56% maturity, approximately 47 months after the first patient is randomised). The interim analyses will be assessed by an IDMC (further details are given in the IDMC charter). It is expected that recruitment will have completed prior to the results of these interim analyses being available.

#### 12.2.16.1 **PFS interim analysis**

Approximately 367 PFS events (52% maturity) will be available for the interim PFS analysis.

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

The criterion for superiority is a statistically significant improvement in PFS at the interim analysis. If 80% of the PFS events required at the time of the primary PFS analysis is available at the time of the interim (ie, 367/458 PFS events have occurred), the 2-sided significance level to be applied for the PFS interim analysis would be 1.04% and the 2-sided significance level to be applied for the primary PFS analysis would be 2.19%.

If the PFS results indicate superiority, then analyses of all other endpoints may also be performed. Patients would continue to be followed for PFS and survival until approximately 458 PFS events, when the primary PFS analysis and the first interim OS analysis would be performed.

If the PFS interim analysis result does not meet the criterion of stopping for superiority, then all patients will remain blinded and continue to be followed for PFS and OS.

The recommendations from the IDMC will not reveal the results of the analysis but will take the form of "Continue/Modify/Stop".

#### 12.2.16.2 **OS interim analyses**

Approximately 285 and 393 death events (41% and 56% maturity) will be available for the first and the second interim OS analysis, respectively (assuming OS HR=0.73).

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

The criterion for superiority is a statistically significant improvement in OS at the interim analyses. If 58% or 80% of OS events required at the time of the primary OS analysis is available at the time of the interim (ie, 285/491 or 393/491 events have occurred), the 2-sided significance level to be applied for the OS interim analysis would be 0.21% and 0.98%, respectively, and the 2-sided significance level to be applied for the primary OS analysis would be 2.17%.

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 approximately 491 patients have died, when an updated analysis would be performed.

If the PFS result is not statistically significant and/or either of the OS interim analysis result does not meet the criterion of stopping for superiority, then all patients will remain blinded and continue to be followed for survival.

The recommendations from the IDMC will not reveal the results of the analysis but will take the form of "Continue/Modify/Recommend Early Submission/Stop".

## 12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The two co-primary endpoints of this study are OS and PFS. To control for type-I error, a significance level of 2.5% will be used for analysis of OS and a significance level of 2.5% will be used for 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.

Approximately 702 patients will be randomised 2:1 to obtain 491 death events in the ITT population (70% maturity). The primary PFS analysis DCO will occur when it is expected that 458 PFS events have occurred (65% maturity). If the true PFS HR is 0.67, the study will provide at least 95% power to demonstrate a statistically significant difference for PFS with a 2-sided significance level of 2.5% in the ITT population; this translates to a 5-month benefit in median PFS over 10 months on placebo if PFS is exponentially distributed. The smallest treatment difference that would be statistically significant is a HR of 0.8. A recruitment period of approximately 22 months and a follow-up period of 14 months are expected for the PFS endpoint. Therefore it is anticipated that this PFS analysis could be performed approximately 36 months after the first patient has been randomised.

The primary OS analysis DCO will occur when it is expected that 491 OS events have occurred (70% maturity). If the true OS HR is 0.73, this number of death events will provide at least 85% power to demonstrate a statistically significant difference for OS, assuming a 2.5% 2-sided significance level in the ITT population; this translates to an 8-month benefit in median OS over 22 months on placebo if OS is exponentially distributed. The smallest treatment difference that would be statistically significant is a HR of 0.81. A recruitment period of approximately 22 months and a follow-up period of 40 months are expected for the OS endpoint. Therefore it is anticipated that this OS analysis could be performed at approximately 62 months after the first patient has been randomised.

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 as well as interim efficacy analyses for superiority based on PFS and OS and the primary analysis of PFS:

- The IDMC will review the safety data from approximately the first 75 patients, or approximately 3 months after randomisation of the first patient and then again 3 months later

- The IDMC will then meet at least every 6months thereafter up to the decision to unblind the study to review safety data

- The IDMC will review the unblinded interim analysis summaries of efficacy data

- Additional reviews of the safety data may be requested by the IDMC at additional points during 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.

In addition:

- The IDMC will review the efficacy data when 367 progression events have occurred, at approximately 30 months post-randomisation, at the time of the interim analysis of PFS.

- The IDMC will review the efficacy data when 458 progression events have occurred, at approximately 36 months post-randomisation at the time of the primary analysis of PFS and the first interim analysis of OS.

- The IDMC will review the efficacy data when 393 OS events have occurred, at approximately 47 months post-randomisation at the time of the second interim analysis of OS.

A separate IDMC charter will be developed, which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

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 IQVIA 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 IQVIA Medical Emergency Contact Centre PPD or alternative number PPD. After final DCO for the study, 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 | IQVIA<br>PPD<br>Livingston EH54 7EG<br>United Kingdom<br>Office: PPD |
| PPD | Study Physician | Astra Zeneca<br>PPD<br>Gaithersburg, MD, 20878<br>USA<br>Office: PPD |
| Patient Safety | AstraZeneca/MedImmune Patient Safety | BUDAPEST:<br>c/o PPD<br>Tata Consultancy Services<br>PPD<br>Budapest - 1117, Hungary<br>MUMBAI:<br>c/o PPD<br>Tata Consultancy Services<br>PPD<br>Thane - West, 400607<br><br>PPD |

## 13.2 Overdose

Use of MEDI4736 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 and possible symptoms of overdose are not established.

- 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 CRF module.

If an overdose on an AstraZeneca/MedImmune study drug occurs in the course of the study and is associated with an SAE, then Investigators or other site personnel inform appropriate AstraZeneca/MedImmune representatives (ie, IQVIA) immediately, or **no later than 24 hours** of when he or she becomes aware of it (see Section 6.4.4).

The designated AstraZeneca/MedImmune representative (ie, IQVIA) works with the Investigator to ensure that all relevant information is provided to the AstraZeneca/MedImmune Patient Safety data entry site.

For all other overdoses ie, those not associated with an SAE, reporting should be done within 30 days.

If an overdose on an AstraZeneca study drug occurs after the final DCO for the study, 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 AstraZeneca/MedImmune representative (ie, IQVIA).

Following the final DCO for the study, 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 investigational product 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, then Investigators or other site personnel inform appropriate AstraZeneca/MedImmune representatives (ie, IQVIA) immediately, or **no later than 24 hours** of when he or she becomes aware of it.

If any pregnancy occurs after the final DCO for the study, 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 final DCO for the study.

### 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 following the last dose.

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 after the last dose should be followed up and documented.

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**Clinical Study Protocol Amendment No 07**
**Appendix A**

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|---|---|
| Drug Substance | MEDI4736 |
| Study Code | D4191C00001 |
| Edition Number | 01 |
| Date | 04 September 2019 |
| Protocol Dated | 07 December 2017 |

# Appendix A
# Signatures

# ASTRAZENECA SIGNATURE(S)

## A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

PPD

PPD

Date
(Day Month Year)

AstraZeneca
Gaithersburg, MD 21228
PPD
USA
Tel: PPD

# ASTRAZENECA SIGNATURE(S)

## A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

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I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

PPD

PPD

Date
(Day Month Year)

IQVIA
PPD
Livingston EH54 7EG
United Kingdom
Office: PPD

## ASTRAZENECA SIGNATURE(S)

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**A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC))**

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This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

PPD

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Cheshire, SK10 2NA
United Kingdom
Tel PPD

# SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

## A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

**AstraZeneca Research and Development site representative**

PPD

Durham, NC 27707
United States

PPD

Date
(Day Month Year)

AstraZeneca

| Clinical Study Protocol Appendix B | |
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| Drug Substance | MEDI4736 |
| Study Code | D4191C00001 |
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| Date | 17 February 2014 |

# Appendix B
# Additional Safety Information

# FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

## Life threatening

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

## Hospitalisation

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

## Important medical event or medical intervention

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

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

Examples of such events are:

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

# A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

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

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

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

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

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

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

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

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

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

| Clinical Study Protocol Appendix C | |
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# Appendix C
# International Airline Transportation Association (IATA) 6.2 Guidance Document

# LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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| **Clinical Study Protocol Appendix D** | |
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| Drug Substance | MEDI4736 |
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# Appendix D
# Pharmacogenetics Research

## TABLE OF CONTENTS PAGE

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| DNA | Deoxyribonucleic acid |
| LIMS | Laboratory information management system |
| NSCLC | Non-Small Cell Lung Cancer |

# 1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the MEDI4736 clinical development program to explore how genetic variations may affect the clinical parameters associated with this drug. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to MEDI4736, but also susceptibility to NSCLC. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to NSCLC and MEDI4736 treatment.

# 2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA, derived from a blood sample, for future exploratory research into genes/genetic variations that may influence response, ie, distribution, safety, tolerability and efficacy of MEDI4736, and/or susceptibility to NSCLC.

# 3. GENETIC RESEARCH PLAN AND PROCEDURES

## 3.1 Selection of genetic research population

### 3.1.1 Study selection record

All enrolled patients who take part in the main study will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

### 3.1.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

### 3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

### 3.1.4 Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

## 3.2 Collection of samples for genetic research

Blood samples will ideally be collected at the Screening Visit. If for any reason the sample is not drawn at the Screening Visit, it should be taken as soon as possible, but not later than the last study visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event, as these patients would be important to include in any genetic analysis. Only 1 sample should be collected per patient for genetics during the study.

If the patient agrees to participate, an 8.5 ml blood sample will be collected into a tube containing reagents that coagulate blood and stabilize blood cell DNA and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be identified with the protocol study number, centre number, enrolment code and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the host genetic research and the date of the blood sample collection will be recorded.

AstraZeneca/MedImmune, or its designee, will act as the central laboratory for sample logistics. This will include the supply of site material and all transport arrangements.

A single blood sample will be stored frozen (-20°C or below) at the site and sent to the central laboratory. The central laboratory will then send the samples to AstraZeneca/MedImmune, or its designee laboratory, for DNA extraction. Samples must remain frozen at all times. Further details on the processing of the samples are outlined in the Laboratory Manual for Investigators.

## 3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca/MedImmune genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca/MedImmune employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

# 4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

## 4.1 Informed consent

The portion of this study evaluating genetic alterations in blood samples is optional and the patient may participate in other components of the main study without participating in this specific genetic analysis. To participate in this genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

## 4.2 Subject data protection

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. Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report. 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 an investigator might know a patient's identity and also have access to his or her genetic data. Regulatory authorities may also require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

# 5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca/MedImmune to analyze the samples.

The results from this genetic research will be reported separately from the clinical study report for the main study.

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.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

# 7. LIST OF REFERENCES

None

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| Revised Clinical Study Protocol Appendix E | |
|---|---|
| Drug Substance | MEDI4736 |
| Study Code | D4191C00001 |
| Edition Number | 01 |
| Date | 08 August 2014 |

# Appendix E
# Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

## TABLE OF CONTENTS PAGE

# 1. INTRODUCTION

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

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

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

# 2. DEFINITIONS

**Potential Hy's Law**

A Potential Hy's Law (PHL) case is defined as a study subject with an increase in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 x upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2 x ULN irrespective of an increase in alkaline phosphatase (ALP) at any point during the study following the start of study medication.

**Hy's Law**

A Hy's Law (HL) case is defined as a study subject with an increase in serum AST or ALT ≥3 x ULN **together with** TBL ≥2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

# 3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥3 x ULN

- AST ≥3 x ULN
- TBL ≥2 x ULN

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

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory case report form (CRF)

# 4. FOLLOW-UP

## 4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

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

## 4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

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

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

# 5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

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

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

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

# 6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment (including the 30 day follow-up period post-discontinuation of study treatment) having previously met PHL criteria at a study visit prior to starting study treatment.

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

- Determine if there has been a significant change in the patients' condition[1] compared with the last visit where PHL criteria were met[1]

  – If there is no significant change no action is required

  – If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 of this Appendix.

[1] A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

# 7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment (including the 90-day follow-up period) and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[2] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix.

# 8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

[2] A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

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**Revised Clinical Study Protocol Appendix F**

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|---|---|
| Drug Substance | MEDI4736 |
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# Appendix F
# Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

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# 1. INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D4191C00001 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

# 2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Patients with measurable disease and/or non measurable and/or no evidence of disease assessed at baseline by computed tomography (CT)/magnetic resonance imaging (MRI) will be entered in this study. RECIST 1.1 has been modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at baseline.

**Measurable:**

A lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements.[1]

**Non-measurable:**

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline[2]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Skin lesions assessed by clinical examination
- Brain metastasis

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1 Localised post-radiation changes which affect lesion sizes may occur and there may be high levels of necrosis/fibrosis with little or no active tumour in recently irradiated lesions. However accepting these limitations in this patient population with prior curative radiation treatment the prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

2 Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions.

**Special cases:**

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs).

**Target lesions:**

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, may be identified as TLs at baseline.

**Non-target lesions:**

All other lesions (or sites of disease) not recorded as TL should be identified as non-target lesions (NTL) at baseline.

# 3. METHODS OF ASSESSMENT

**The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.**

A summary of the methods to be used for RECIST assessment is provided in Table 1 and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

**Table 1 Summary of methods of assessment**

| Target lesions | Non-target lesions | New lesions |
|---|---|---|
| CT (preferred) | CT (preferred) | CT (preferred) |
| MRI | MRI | MRI |
| | Clinical examination | Clinical examination |
| | X-ray, Chest X-ray | X-ray, Chest X-ray |
| | | Ultrasound |
| | | Bone scan |

CT Computed tomography; MRI Magnetic resonance imaging.

## 3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D4191C00001 study it is recommended that CT examinations of the chest and abdomen, (including liver and adrenal glands) will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

## 3.2 Clinical examination

In the D4191C00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

## 3.3 X-ray

### 3.3.1 Chest X-ray

In the D4191C00001 study, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

### 3.3.2 Plain X-ray

In the D4191C00001 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

## 3.4 Ultrasound

In the D4191C00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

## 3.5 Endoscopy and laparoscopy

In the D4191C00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

## 3.6 Tumour markers

In the D4191C00001 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

## 3.7 Cytology and histology

In the D4191C00001 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

## 3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D4191C00001 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

## 3.9 18-Fluoro-deoxyglucose positron emission tomography (FDG PET) scan

In the D4191C00001 study, FDG-PET scans will not be used as the sole method for identifying new lesions due to the inflammatory changes due chemoradiation therapy resulting in increased FDG uptake on a baseline scan performed within the Screening period for this study.

# 4. TUMOUR RESPONSE EVALUATION

## 4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of MEDI4736/placebo (see Table 1 in the Clinical Study Protocol), and ideally as close as possible before the start of study drug. Follow-up assessments will be performed every 8 weeks for the first 12 months (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 study drug/or subsequent therapy).

Additional assessments will be performed post-confirmed objective disease progression for patients remaining on study treatment, re-treatment or until subsequent cancer therapy according to the Clinical Study Protocol.

Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

## 4.2 Target lesions

### 4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved may be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

**Special cases:**

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery, during the study, the size of the TL should still be provided where possible.

### 4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL (see Table 2).

**Table 2 Evaluation of target lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD |
| Progression of disease (PD) | At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. |
| Not Evaluable (NE) | Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response |

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

## 4.3 Non-target lesions

### 4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 3).

**Table 3 Evaluation of non-target lesions**

| | |
|---|---|
| Complete response (CR) | Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis). |
| Non CR/Non PD | Persistence of one or more NTL. |
| Progression (PD) | Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy. |
| Not evaluable (NE) | Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit.<br>Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met. |

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

## 4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

## 4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

## 4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 4.

**Table 4 Overall visit response**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | NA | No | CR |
| NA | CR | No | CR |
| CR | Non CR/Non PD | No | PR |
| CR | NE | No | PR |
| PR | Non PD or NE | No | PR |
| SD | Non PD or NE | No | SD |
| NA | Non CR/Non PD | No | SD (Non CR/Non PD) |
| NE | Non PD or NE | No | NE |
| NA | NE | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |
| NA | NA | No | NED |

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NA Not applicable (only relevant if there were no target lesions/non-target lesions at baseline), NE Not evaluable, NED No evidence of disease.

# 5. CONFIRMATION OF PROGRESSION

Disease progression requires confirmation, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progression of disease (PD) in the absence of clinical deterioration.

Progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits (with an absolute increase of at least 5 mm)
- and/or significant progression (worsening) of non TLs or new lesions at the confirmatory PD time-point compared with the first time point where progression of NTLs or new lesions identified
- and/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first time point new lesions identified.

In the absence of significant clinical deterioration the investigator should continue study treatment until progression is confirmed.

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 objective disease progression.

# 6. CENTRAL REVIEW

The Contract Research Organisation appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

# 7. REFERENCES

**Eisenhauer et al 2009**
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009 Jan;45(2):228-47.

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| Clinical Study Protocol Appendix G | |
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# Appendix G
# Patient Reported Outcomes: EORTC-QLQ-C30, LC-13 and EQ-5D-5L

# EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

# EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| **During the past week :** | | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|---|
| 31. | How much did you cough? | 1 | 2 | 3 | 4 |
| 32. | Did you cough up blood? | 1 | 2 | 3 | 4 |
| 33. | Were you short of breath when you rested? | 1 | 2 | 3 | 4 |
| 34. | Were you short of breath when you walked? | 1 | 2 | 3 | 4 |
| 35. | Were you short of breath when you climbed stairs? | 1 | 2 | 3 | 4 |
| 36. | Have you had a sore mouth or tongue? | 1 | 2 | 3 | 4 |
| 37. | Have you had trouble swallowing? | 1 | 2 | 3 | 4 |
| 38. | Have you had tingling hands or feet? | 1 | 2 | 3 | 4 |
| 39. | Have you had hair loss? | 1 | 2 | 3 | 4 |
| 40. | Have you had pain in your chest? | 1 | 2 | 3 | 4 |
| 41. | Have you had pain in your arm or shoulder? | 1 | 2 | 3 | 4 |
| 42. | Have you had pain in other parts of your body? | 1 | 2 | 3 | 4 |
| | If yes, where _____ | | | | |
| 43. | Did you take any medicine for pain? | | | | |
| | **1 No 2 Yes** | | | | |
| | If yes, how much did it help? | 1 | 2 | 3 | 4 |


## Health Questionnaire

## English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐