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**Revised Clinical Study Protocol 4**

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|---|---|
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# A Phase II, Non-comparative, Open label, Multi-centre, International Study of MEDI4736, in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV) who have received at least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen (ATLANTIC)

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**AstraZeneca Research and Development site representatives**

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

| Amendment No. | Date of Amendment | Local Amendment No: | Date of Local Amendment |
|---|---|---|---|
| 1 | | | |
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| Administrative Change No. | Date of Administrative Change | Local Administrative Change No. | Date of Local Administrative Change |
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| 1 | | | |
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**PROTOCOL SYNOPSIS**

# A Phase II, Non-comparative, Open label, Multi-centre, International Study of MEDI4736, in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB-IV) who have received at least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen (ATLANTIC)

**International Co-ordinating Investigator**

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

This study will consist of 3 cohorts:

- Cohort 1 will include patients who have epidermal growth factor receptor (*EGFR*) tyrosine kinase (TK) mutations or anaplastic lymphoma kinase (ALK) alterations (hereafter referred to as *EGFR*/*ALK* positive) and whose tumour tissue samples have ≥25% of tumour cells with membrane staining for PD-L1 (referred to as PD-L1 positive).

- Cohort 2 will include patients who do not have *EGFR* TK mutations or *ALK* alterations and patients whose *EGFR* TK mutation status or *ALK* fusion status is unknown (hereafter referred to as *EGFR*/*ALK* wild type) and whose tumour tissue samples have ≥25% of tumour cells with membrane staining for PD-L1 (referred to as PD-L1 positive).

- Cohort 3, which will start recruiting once Cohort 2 has finished recruitment, will include patients who are *EGFR/ALK* wild type and whose tumour tissue samples have ≥90% of tumour cells with membrane staining for PD-L1.

The number of patients within Cohort 2 with ≥90% of tumour cells with membrane staining will not be known during recruitment. Each of the 3 cohorts will contain approximately 94 patients with tumours prospectively determined to be PD-L1 positive (as defined above). As the diagnostic to determine PD-L1 status was not available when the study first started there will be a number of patients in Cohorts 1 and 2 with tumours determined to be PD-L1 negative and positive (and possibly unknown) (based retrospectively on the patient's pre-treatment tumour sample). All patients, regardless of tumour PD-L1 status, will continue to be treated with MEDI4736 per protocol.

Approximately 700 patients will be enrolled in Cohorts 1, 2 and another 700 patients in Cohort 3.

Approximately 700 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC; Stage IIIB-IV) will be enrolled and undergo a pre-screening assessment on their tumour tissue sample to determine programmed death ligand 1 (PD-L1) status. On the assumption that approximately 30% of patients from this population have tumours that are PD-L1 positive (AstraZeneca, unpublished data), where positive is defined as ≥25% of tumour cells with membrane staining (proprietary PD-L1 immunohistochemistry assay; ), it is anticipated that about 210 of the 700 pre-screened patients will have PD-L1 positive tumours and that 188 of these will go on to receive MEDI4736 in Cohorts 1 and 2 at 100 to 150 sites in North America, Asia, and Europe.

An additional group of patients with locally advanced or metastatic NSCLC will be enrolled and undergo a pre-screening assessment on their tumour tissue sample to identify patients who possess PD-L1 positive tumours, with ≥90% of tumour cells with membrane staining (using the same proprietary assay). On the assumption that approximately 15% of patients from the advanced/metastatic NSCLC population have tumours that meet this threshold (AstraZeneca, unpublished data), it is anticipated that, additionally, about 105 of 700 pre-screened patients will have ≥90% of tumour cells with membrane staining and that 94 of these will go on to receive MEDI4736 in Cohort 3.

| **Study period** | | **Phase of development** |
|---|---|---|
| Estimated date of first patient enrolled | Q2 2014 | 2 |
| Estimated date of last patient completed | Q3 2017 | 2 |

## Objectives

| Primary Objective: | Outcome Measure: |
|---|---|
| Cohort 1<br>To assess the efficacy of MEDI4736 treatment in terms of ORR in PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>Cohort 2<br>To assess the efficacy of MEDI4736 treatment in terms of ORR in PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>Cohort 3<br>To assess the efficacy of MEDI4736 treatment in terms of ORR in PD-L1 positive patients with ≥90% of tumour cells with membrane staining | ORR using Independent Central Review assessments according to RECIST 1.1[a,b] |

a The primary analysis of ORR will be based on programmatically derived ORR based upon Independent Central Review assessment. Sensitivity analyses of ORR will also be performed based on tumour information recorded in the clinical database by the investigator according to RECIST 1.1 and upon ORR based on Independent Central Review assessment according to RECIST 1.1 modified for confirmation of progression.

b Objective tumour response (complete response or partial response) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

ORR Objective response rate; PD-L1 Programmed death ligand 1; RECIST Response Evaluation Criteria In Solid Tumours.

| Secondary Objective: | Outcome Measure: |
|---|---|
| Cohort 1<br>To further assess the efficacy of MEDI4736 in terms of: DoR, DCR, TTR, PFS and OS in PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>Cohort 3<br>To further assess the efficacy of MEDI4736 in terms of: DoR, DCR, TTR, PFS and OS in PD-L1 positive patients with ≥90% of tumour cells with membrane staining | DoR using Independent Central Review assessments according to RECIST 1.1[a]<br>DCR using Independent Central Review assessments according to RECIST 1.1[a]<br>TTR using Independent Central Review assessments according to RECIST 1.1[a]<br>PFS using Independent Central Review assessments according to RECIST 1.1[a]<br>OS |
| Cohort 2<br>Key secondary objectives:<br>To assess the efficacy of MEDI4736 in terms of ORR in<br>• Non-squamous PD-L1 positive (≥25% of tumour cells with membrane staining) patients<br>• PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br>• Non-squamous PD-L1 positive patients with ≥90% of tumour cells with membrane staining | ORR using Independent Central Review assessments according to RECIST 1.1[a,b]<br>DoR using Independent Central Review assessments according to RECIST 1.1[a]<br>DCR using Independent Central Review assessments according to RECIST 1.1[a]<br>TTR using Independent Central Review assessments according to RECIST 1.1[a]<br>PFS using Independent Central Review assessments according to RECIST 1.1[a]<br>OS |

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| Other secondary objectives:<br>To further assess the efficacy of MEDI4736 in terms of: DoR, DCR, TTR, PFS and OS in<br>• PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>• Non-squamous PD-L1 positive (≥25% of tumour cells with membrane staining) patients<br>• PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br>• Non-squamous PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br><br>To assess the efficacy of MEDI4736 in<br>• PD-L1 negative patients (<25% of tumour cells with membrane staining)<br>• Non-squamous PD-L1 negative (<25% of tumour cells with membrane staining) patients<br>• PD-L1 unselected patients (combined population of PD-L1 positive, PD-L1 negative and PD-L1 unknown patients who were enrolled under the original protocol [ie, prior to the amendment to only enrol PD-L1 positive patients])<br>• Patients with <90% of tumour cells with PD-L1 membrane staining<br>• Non-squamous patients with <90% of tumour cells with PD-L1 membrane staining | |
| Cohorts 2 and 3<br>To assess the efficacy of MEDI4736 in a combined population of Cohorts 2 and 3 for:<br>• PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br>• Non-squamous PD-L1 positive patients with ≥90% of tumour cells with membrane staining | ORR using Independent Central Review assessments according to RECIST 1.1<br>DoR using Independent Central Review assessments according to RECIST 1.1<br>DCR using Independent Central Review assessments according to RECIST 1.1<br>TTR using Independent Central Review assessments according to RECIST 1.1<br>PFS using Independent Central Review assessments according to RECIST 1.1<br>OS |
| All cohorts<br>To assess the safety and tolerability profile of MEDI4736 | AEs, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, haematology and urinalysis |
| All cohorts<br>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) |

| Secondary Objective: | Outcome Measure: |
|---|---|
| All cohorts<br>To investigate the immunogenicity of MEDI4736 | ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed]) |

a Analysis of ORR, DoR, DCR, TTR and PFS and will be based upon Independent Central Review assessment. For the analyses to be conducted, see the statistical methods section.
b Objective tumour response (complete response or partial response) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

ADA Anti-drug antibody; AE Adverse event; DCR Disease control rate; DoR Duration of response; ORR Objective response rate; OS Overall survival; PD-L1 Programmed death ligand 1; PFS Progression free survival; PK Pharmacokinetic(s); RECIST Response Evaluation Criteria In Solid Tumours; TTR Time to response.

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To explore immune-related response criteria as an assessment methodology for clinical benefit of MEDI4736 by Independent Central Review | ORR, DoR, DCR, TTR and PFS using Independent Central Review assessments according to immune-related response criteria |
| 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 collect blood and tissue samples for analysis of biomarkers including but 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 | Biomarker analysis of blood and tissue to assess exploratory markers including 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 before and after treatment with MEDI4736 and MEDI4736 PK exposure, clinical outcomes, efficacy, AEs and/or safety parameters | 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 treatments and/or susceptibility to disease (optional) | Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response parameters observed in patients treated with MEDI4736 and/or susceptibility to disease |
| To assess the efficacy in PD-L1 negative patients (where negative is defined as <25% of tumour cells with membrane staining) in Cohort 1 (if there are sufficient patients) and additionally, in all patients in a combined population of Cohorts 1 and 2 | ORR, DoR PFS (using Independent Central Review assessments according to RECIST 1.1) and OS. |

AE Adverse event; DCR Disease Control Rate; DoR Duration of response; IFN Interferon; IL Interleukin; ORR Objective response rate; OS Overall survival; PD-L1 Programmed death ligand 1; PFS Progression free survival; PK Pharmacokinetic(s); T-cell T lymphocyte; TTR Time to response.

**Study design**

This study is a Phase II, non-comparative, open label, multi-centre study assessing the efficacy and safety of MEDI4736 in the treatment of male and female patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) that is PD-L1 positive who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen.

Patients will undergo a pre-screening assessment on their tumour tissue sample to determine PD-L1 status. Approximately 188 patients with tumours that are PD-L1 positive (≥25% of tumour cells with membrane staining: 94 patients who are *EGFR/ALK* positive and 94 patients who are *EGFR/ALK* wild type), and an additional 94 patients with *EGFR/ALK* wild type and ≥90% of tumour cells with membrane staining for PD-L1 will be treated with MEDI4736 (10 mg/kg every 2 weeks [Q2W] intravenous [iv]) for 12 months. In addition, patients with tumours that are PD-L1 negative, who were recruited prior to the availability of a PD-L1 diagnostic, will continue to be treated.

Tumour assessments will be performed using computed tomography/magnetic resonance imaging. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks for the first 48 weeks (relative to the date of the first infusion) 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 treatment/or subsequent therapy). An exception are patients with confirmed progression of disease (PD) that continue to receive MEDI4736 at the discretion of the investigator (after consultation with the sponsor); these patients can receive treatment for a maximum of 12 months and will have scans every 8 weeks until study treatment is stopped. 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.

Categorisation of objective tumour response assessment will be based on RECIST 1.1: complete response (CR), partial response (PR), stable disease (SD) and PD. RECIST 1.1 measurements will be used to programmatically derive the primary variable of objective response rate (ORR) and secondary variables of duration of response (DoR), disease control rate (DCR), time to response (TTR) and progression free survival (PFS). Objective tumour response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

All scans showing PD should be confirmed preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with MEDI4736 will continue between the initial assessment of progression and confirmation for progression. In the absence of clinically significant 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 confirmed objective disease progression.

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month MEDI4736 treatment period may restart treatment with MEDI4736 upon evidence of PD, with or without confirmation, during follow-up. To restart treatment the patient must not have received an intervening systemic anti-cancer therapy post-MEDI4736 discontinuation. Patients should have a baseline tumour assessment within 28 days of restarting treatment with MEDI4736, all further scans should occur every 8 weeks (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

Patients with confirmed PD that continue to receive MEDI4736 at the discretion of the investigator (after consultation with the sponsor) can do so for a maximum of 12 months. Patients will have scans every 8 weeks while on treatment (relative to the date of the first infusion) until study treatment is stopped.

Patients with confirmed PD that discontinue MEDI4736, should have scans conducted according to local practice and submitted for Independent Central Review (ICR) until the patient commences a new treatment (these scans are optional).

Following completion or discontinuation of treatment, patients will enter a follow-up period.

**Target patient population**

Male or female patients aged 18 years or older with histologically-documented or cytologically-documented Stage IIIB/Stage IV NSCLC (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) that is PD-L1 positive, or with recurrent or PD following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease). Patients with advanced or metastatic NSCLC must have received at least 2 prior systemic treatment regimens to be eligible including a platinum-based chemotherapy regimen. Patients must have World Health Organisation Performance Status of 0 or 1. In addition, a number of patients with tumours that are PD-L1 negative, who were recruited prior to the availability of a PD-L1 diagnostic, will be included.

All patients entering the study should have known *EGFR* TK mutation or *ALK* fusion status. Cohort 1 will include PD-L1 positive patients (≥25% of tumour cells with membrane staining) who are *EGFR/ALK* positive. Cohort 2 will include PD-L1 positive patients (≥25% of tumour cells with membrane staining) with *EGFR/ALK* wild type status (ie, patients do not have *EGFR* TK mutations or *ALK* alterations). Cohort 3 will include PD-L1 positive patients with *EGFR/ALK* wild type status and ≥90% of tumour cells with membrane staining. In the event that no valid test result is available, eligible patients with unknown *EGFR* TK mutation or *ALK* fusion status will be enrolled into the *EGFR/ALK* wild type cohort that is open for enrolment at that time (recruitment to Cohort 3 will not commence until recruitment to Cohort

2 has been completed). Only those patients with a tumour that is determined to be PD-L1 positive from a central test will be permitted into the study. In the case of those patients who have already been recruited prior to the availability of the PD-L1 diagnostic, a PD-L1 status can be determined retrospectively based on the patient's pre-treatment tumour sample. The PD-L1 testing will take place in the pre-screening period and be on either an archival sample or a recent tissue biopsy.

As the diagnostic to determine PD-L1 status was not available when the study first started there will be a number of patients in Cohorts 1 and 2 with tumours determined to be PD-L1 negative and positive (and possibly unknown) (based retrospectively on the patient's pre-treatment tumour sample). All patients, regardless of tumour PD-L1 status, will continue to be treated with MEDI4736 per protocol. The analysis of PD-L1 positive patients in Cohorts 1 and 2 will include all patients, regardless of whether their PD-L1 status was determined prospectively or retrospectively.

For patients who are treated through progression or patients who achieve disease control at 12 months and restart treatment upon evidence of PD, with or without confirmation, during follow-up, the investigator should ensure these patients still meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in the protocol for this study including re-consenting to treatment. These 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 for continuing MEDI4736.

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

Patients will receive MEDI4736 10 mg/kg via a 60-minute iv infusion Q2W ±3 days.

**Comparator, dosage and mode of administration**

Not applicable.

**Duration of treatment**

Treatment with MEDI4736 will commence on Day 1 following confirmation of eligibility and will continue on a Q2W schedule for a maximum duration of treatment of 12 months. The final administration of MEDI4736 will be at the Week 50 visit. Study treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

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

Disease progression requires confirmation; treatment with MEDI4736 will continue between the initial assessment of progression and confirmation for progression. If progression is not confirmed then the patient should continue on study treatment and on treatment assessments.

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month MEDI4736 treatment period will enter follow-up. Upon evidence of PD (with or without confirmation) following discontinuation of 12 months of treatment, patients may restart treatment with MEDI4736 for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Patients will only be able to restart treatment once; thus a maximum of two 12-month periods will be allowed.

Patients who have confirmed PD during the 12-month initial treatment period or in the 12-month period after restarting MEDI4736 and cannot continue to receive MEDI4736, will enter follow-up for 90-day safety assessments and further survival follow-up.

Patients with confirmed PD that continue to receive MEDI4736 at the discretion of the investigator can receive treatment for a maximum of 12 months.

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

**Outcome variable(s)**

See Objectives.

**Statistical methods**

*General methods applicable to all cohorts:*

The primary objective of this study is to assess the efficacy in terms of ORR of MEDI4736 treatment. Objective response rate (per RECIST 1.1 as assessed by the ICR) is defined as the number (%) of patients with a confirmed response of CR or PR and the primary analysis in each cohort will be based on all treated patients with measurable disease at baseline per the ICR in the primary analysis population of the cohort.

Based upon approximately 80 patients having baseline measurable disease per the ICR in any given cohort (from a total of 94 patients per cohort having measurable disease at baseline per the site investigator), a 2-sided exact 95% confidence interval (CI) for the ORR will be (16.0%, 35.9%) provided the observed ORR is 25.0% (based upon 20 patients responding out of 80 patients). Similarly, if the observed ORR is 40.0% (based upon 32 patients responding out of 80 patients) then a 2-sided 95% CI for the ORR will be (29.2%, 51.6%). Secondary efficacy variables include: DoR, DCR, TTR, PFS and overall survival (OS).

For each cohort, the data cut-off (DCO) for the primary efficacy analysis will take place approximately 24 weeks after the last patient is enrolled into the cohort.

The final analysis of OS (secondary endpoint) will take place approximately 12 months after the last patient is enrolled into each cohort.

The ORR will be estimated with 95% exact CIs. The primary analysis will be based on the programmatically derived ORR based on ICR assessments using RECIST, and using all scans regardless of whether they were scheduled or not. Sensitivity analyses of ORR from the site investigator tumour data will also be performed according to RECIST 1.1 and additionally from the ICR according to RECIST modified for confirmation of progression and irRECIST. In addition, a sensitivity analysis will be performed upon all treated patients who have a baseline tumour assessment and have measurable disease at baseline according to the investigator. Other major efficacy endpoints using RECIST data based upon the ICR assessments will also have sensitivity analyses performed.

Kaplan-Meier plots of DoR, PFS (both of which will be programmatically derived based on ICR using RECIST) and OS will be presented. Summaries of the number and percentage of patients experiencing a PFS or OS event will be provided. Median DoR, PFS and OS will be summarised. The DCR (obtained from programmatic derivations based on ICR assessments using RECIST) will be summarised (ie, number of patients [%] for each cohort). The TTR (obtained from programmatic derivations based on ICR assessments using RECIST) will also be summarised (ie, number of patients [%] for each cohort) for each scheduled timepoint. Sensitivity analyses will also be performed from the site investigator tumour data according to RECIST 1.1 and from data obtained from the ICR using immune-related response criteria (irRECIST).

Generally, all analyses and reporting will be separated for each cohort. However, an exploratory analysis will be undertaken where Cohorts 1 and 2 are combined. It is anticipated that Cohort 2 will be analysed first, followed by Cohort 1 and then, finally, Cohort 3. In addition to presentation for each cohort, the safety data may be aggregated and presented overall at the time of the reporting of the second and third cohorts. Exploratory testing of biological samples will be conducted after patients have entered this study, and this may include testing for *EGFR* mutation/*ALK* fusion status. If a patient entered the study with unknown *EGFR* TK mutation/*ALK* fusion status and is subsequently found to be *EGFR*/*ALK* positive, and during their treatment history they have received an EGFR or ALK TKI, they will be re-assigned to the *EGFR/ALK* positive cohort for the final data analysis. Patients with unknown status who are found to be *EGFR/ALK* positive but who have not received an EGFR or ALK TKI prior to entering the study will remain in the *EGFR/ALK* wild type cohort.

Summaries of MEDI4736 pharmacokinetic exposure data will be provided for all evaluable patients.

Summaries of immunogenicity data will be provided for the number and percentage of patients who develop detectable anti-MEDI4736 antibodies.

Safety data will be summarised descriptively and will not be formally analysed. This will be based on the safety analysis set.

Exploratory biomarker and pharmacogenetics research will be reported outside the Clinical Study Report.

*Methods specific to Cohort 2:*

In Cohort 2, ORR in the PD-L1 positive (≥25% of tumour cells with membrane staining) group is the primary endpoint. Objective response rate in the non-squamous PD-L1 positive (≥25% of tumour cells with membrane staining) group, the ≥90% PD-L1 positive group and the non-squamous ≥90% PD-L1 positive group are key secondary endpoints.

An interim analysis of Cohort 2 will be performed after all patients have received one dose of study therapy. This analysis will include preliminary evaluation of efficacy and safety results on PD-L1 positive treated patients. Furthermore, efficacy analysis will also be performed for non-squamous PD-L1 positive patients, the ≥90% PD-L1 positive patients and the non-squamous ≥90% PD-L1 positive patients.

Additional interim analyses may also be conducted after a minimum follow-up of 8 and 12 weeks respectively from the last treated patient in Cohort 2. The primary efficacy analysis population for these analyses will be the treated PD-L1 positive patients with measurable disease at baseline per the ICR who have had an opportunity of being followed up for at least 24 weeks by the interim analysis DCO. A supportive efficacy analysis will be based on the treated PD-L1 positive patients with measurable disease at baseline per the ICR who have had an opportunity of being followed up for at least 16 weeks by the interim analysis DCO. The interim analysis will be performed on ORR, DoR, DCR, TTR, PFS, OS and key safety endpoints.

The purpose of these interim analyses will be for early evaluation of efficacy and safety data for potential interactions with regulatory agencies on future development of MEDI4736. There are no plans to stop the study early based on these interim results and no formal statistical adjustments are planned. The primary efficacy analysis will take place approximately 24 weeks after the last patient is enrolled into the cohort.

Separate interim analysis of the combined population of Cohorts 2 and 3 for ≥90% PD-L1 positive patients will be performed after approximately 100 patients in this group have had the opportunity to be followed up for at least 8 weeks. At this time similar analysis will be performed for the non-squamous ≥90% PD-L1 positive patients. These analyses will follow a similar approach to that mentioned above for the Cohort 2 interim analyses performed at the 8 and 12 week minimum follow-up periods.

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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 |
| ALK | Anaplastic lymphoma kinase |
| ALT | Alanine aminotransferase |
| APC | Antigen presenting cell |
| APF6 | Alive and progression free at 6 months |
| APF12 | Alive and progression free at 12 months |
| APTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| BoR | Best objective response |
| BP | Blood pressure |
| B7-H1 | B7 homolog 1 |
| CD | Cluster of differentiation |
| CI | Confidence interval |
| CL | Clearance |
| CR | Complete response |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Event |
| CTLA-4 | Cytotoxic T-lymphocyte antigen 4 |
| Cyno | Cynomolgus monkey |
| DCR | Disease control rate |
| DLT | Dose limiting toxicity |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of response |

| Abbreviation or special term | Explanation |
|---|---|
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EGFR | Epidermal growth factor receptor |
| FDA | Food and Drug Administration |
| FTIH | First-Time-In-Human |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| hCG | Human chorionic gonadotropin |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICR | Independent Central Review |
| IFN | Interferon |
| Ig | Immunoglobulin |
| IL | Interleukin |
| 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 |
| 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 |
| LIMS | Laboratory Information Management System |
| LFT | Liver function test |
| LLN | Lower limit of normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |

| Abbreviation or special term | Explanation |
|---|---|
| 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 |
| PD | Progression of disease |
| PD-1 | Programmed death 1 |
| PD-L1 | Programmed death ligand 1 |
| PFS | Progression free survival |
| PGx | Pharmacogenetic(s) |
| PK | Pharmacokinetic(s) |
| PR | Partial response |
| Q2W | Every 2 weeks |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| 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 |
| TK | Tyrosine kinase |
| TKI | Tyrosine kinase inhibitor |
| T-cell(s) | T lymphocyte(s) |
| TSH | Thyroid stimulating hormone |
| TTR | Time to response |
| ULN | Upper limit of normal |
| US | United States |

| Abbreviation or special term | Explanation |
|---|---|
| WHO | World Health Organisation |

# 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. Unfortunately, at the time of diagnosis, approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of patients with early stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005).

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

Common third-line treatment for NSCLC in major global markets includes: vinorelbine (NAVELBINE®), tyrosine kinase inhibitors (TKIs such as erlotinib [TARCEVA®] and gefitinib [IRESSA®]), pemetrexed (ALIMTA®), docetaxel (TAXOTERE®), and gemcitabine (GEMZAR) (Decisions Resources 2013). However, there is not enough evidence to make a recommendation for or against using a cytotoxic drug as a third-line therapy. For these patients, clinical trials, experimental treatment, or best supportive care are among the considered treatment options (Azzoli et al 2009, Syrigos et al 2011).

### 1.1.2 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):

1. 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).

2. 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.

3. 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 (Nomi et al 2007, Loos et al 2008, 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 assessments of expression of PD-L1 on the surface of human tumours 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 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 1 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).

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

A Phase 1 clinical study of the anti-PD-1 antibody BMS-936558 (MDX-1106) was conducted in 39 patients (Brahmer et al 2010). No dose limiting toxicities (DLTs) were observed and a maximum tolerated dose (MTD) was not identified. Efficacy data for BMS-936558 (MDX-1106) 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 1 study of BMS-936558 (MDX-1106) 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 1 and 2 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 from a 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 1 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.

Unpublished 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 1 study of MPDL3280A, has also been presented (Herbst et al 2013). In this ongoing study, the most frequently reported AEs, regardless of causality, were fatigue (43%), cough (26%), diarrhoea (26%), nausea (25%), decreased appetite (25%), headache (25%), constipation (23%), dyspnoea (23%), pyrexia (22%), arthralgia (19%), rash (18%), and insomnia (18%). Grade 3

or 4 treatment-related AEs were reported in 13% of patients. No DLTs were observed and an MTD was not identified.

Studies of other agents targeting the PD-1/PD-L1 pathway are also in early stage development with limited data available. CT-011 (anti-PD-1 monoclonal antibody) has been evaluated in a Phase 1 study in advanced hematologic 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. AMP-224, an anti-PD-1 fusion protein, is also being evaluated in Phase 1 clinical studies. However, no clinical data are available at this time.

### 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 IgG1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma receptors involved in triggering effector function.

#### 1.1.3.1 Non-clinical experience with MEDI4736

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

#### 1.1.3.2 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. As of July 2015, a total of 1883 patients have been enrolled and treated with MEDI4736 in 30 ongoing sponsor and collaborative clinical studies: 13 employing MEDI4736 as monotherapy and 17 as combination therapy. No studies have yet been completed.

The majority of the safety data currently available for MEDI4736 are based on the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108 [hereafter referred to as Study 1108]) in patients with advanced solid tumours. As of 14 July 2014, a total of 414 patients have entered into this study of which 393 have received MEDI4736 at 10 mg/kg given every 2 weeks (Q2W). Overall, the most frequently reported (≥ 10% of subjects) AEs (all grades) were fatigue, nausea, dyspnoea, decreased appetite, constipation, diarrhoea, vomiting, cough, pyrexia, back pain, and rash.

Approximately half (48.1%) of these AEs were Grade 1 to 2 in severity and manageable by general treatment guidelines as described in the current MEDI4736 study protocols. Grade 3 or higher AEs were noted in 141 of 393 subjects (35.9%). These events occurring in more than 1% of subjects were dyspnoea (5.1%); increased gamma-glutamyl transferase (3.3%); fatigue, general physical health deterioration, increased aspartate aminotransferase, and back

pain (2.3% each); anaemia and dehydration (1.8% each); and abdominal pain, vomiting, sepsis, syncope, and hypotension (1.3% each).

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

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

Overall, a low incidence of anti-drug antibody (ADA) has been observed. Of the 220 patients who received MEDI4736 monotherapy and for whom PK/ADA data were available as of July 2014, 5 were detected to be ADA positive, with an impact on PK/pharmacodynamics reported in 1 patient.

Data presented at ESMO 2014 with a later cut off of 21 August 2014 showed that MEDI4736 was well tolerated at all doses in the NSCLC subset of patients enrolled into Study 1108 (n=190): drug-related Grade ≥3 AEs were reported in 3% of patients; drug-related AEs leading to discontinuation were reported in 1% of patients; there was no drug-related colitis or hyperglycaemia of any grade; no Grade ≥3 pneumonitis was reported; no drug-related AEs leading to death were reported (Antonia et al 2014).

Efficacy data on MEDI4736 monotherapy in NSCLC patients from Study 1108 presented at ESMO 2014 showed an ORR of 16% in the overall NSCLC patient population (n=162) and a 25% ORR in the PD-L1-positive (≥25% of tumour cells with membrane staining for PD-L1) subset of patients (n=48) (Antonia et al 2014). Updated safety and efficacy data from Study 1108 was presented at international oncology conferences (Rizvi et al 2015 ASCO).

Complete updated data on MEDI4736 is found in the IB.

### 1.1.4 Safety pharmacology summary

At the time of writing this protocol, there have been no AEs or reactions that have an established causal relationship with MEDI4736. (Refer to the latest version of the IB for the latest information.)

However, 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.

Updated information on the safety and efficacy profile of MEDI4736 are provided in the current MEDI4736 IB.

### 1.1.5 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) is efficacious in the treatment of patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) that is PD-L1 positive who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen.

This will be assessed via the primary objective of this study, which is to assess the efficacy of MEDI4736 treatment in terms of ORR. Secondary efficacy objectives include evaluation of duration of response (DoR), disease control rate (DCR), time to response (TTR), progression free survival (PFS) and overall survival (OS). Other secondary objectives include an assessment of safety and tolerability, MEDI4736 PK exposure, immunogenicity, and biomarker status. 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

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

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.

In addition, although clinical experience with MEDI4736 is limited, currently available data from the MEDI4736 FTIH study (Section 1.1.3.2), indicates encouraging response rates and DoR, with a manageable safety profile in patients with a variety of solid malignancies, including patients with advanced NSCLC.

## 1.4 Benefit/risk and ethical assessment

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

Lung cancer is an aggressive, heterogeneous, and complex disease that is often detected at an advanced stage, with no curable option for the majority of patients. Despite advances in the diagnosis, imaging, staging and treatment of NSCLC, the estimated overall 5-year survival for patients in Europe continues to be low (11%) and the outlook for those with refractory advanced NSCLC is extremely poor (D'Addario et al 2010,Hanna et al 2004). Common third-line treatment for NSCLC in major global markets includes: vinorelbine, TKIs and gemcitabine (Decisions Resources 2013). However, there is not enough evidence to make a recommendation for or against using a cytotoxic drug as a third-line therapy. For these patients, clinical trials, experimental treatment, or best supportive care are among the considered treatment options (Azzoli et al 2009, Syrigos et al 2011).

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 recombinant PD-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.

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 FTIH, single agent study (Study 1108) in patients with advanced solid tumours. As of 14 July 2014, a total of 414 patients have entered into this study of which 393 have received MEDI4736 at 10 mg/kg given every 2 weeks (Q2W). Overall, the most frequently reported (≥ 10% of subjects) AEs (all grades) were fatigue, nausea, dyspnoea, decreased appetite, constipation, diarrhoea, vomiting, cough, pyrexia, back pain, and rash.

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

No DLTs have been reported (for further details on the safety data on MEDI4736, please refer to the current IB).

Data presented at ESMO 2014 with a later cut off of 21 August 2014 showed that MEDI4736 was well tolerated at all doses in the NSCLC subset of patients enrolled into Study 1108 (n=190): drug-related Grade ≥3 AEs were reported in 3% of patients; drug-related AEs leading to discontinuation were reported in 1% of patients; there was no drug-related colitis or hyperglycaemia of any grade; no Grade ≥3 pneumonitis was reported; no drug-related AEs leading to death were reported (Antonia et al 2014). More recent data has been presented at international oncology conferences (Rizvi et al 2015 ASCO). Please refer to latest MEDI4736 IB for complete details of efficacy of MEDI4736 across all clinical programs.

Potential risks based on the mechanism of action of MEDI4736 and related molecules include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity, endocrinopathy, pneumonitis and neuropathy.

Other monoclonal antibodies targeting the PD-1/PD-L1 pathway are currently in clinical development. Among the most frequent treatment-related AEs noted with these antibodies are fatigue, rash, diarrhoea and pruritus. Reported immune-mediated AEs of ≥Grade 3 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 3 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, YERVOY™ prescribing information, OPDIVO® prescribing information, KEYTRUDA® prescribing information). 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.

Evidence of clinical activity has also been observed with MEDI4736. Of the 414 patients treated with MEDI4736 (all dose levels), 169 patients were evaluable for response analysis, which included patients who had at least 24 weeks of follow-up as of 14 July 2014 and had either at least 1 post-baseline tumour assessment or experienced clinical progression of disease (PD) or death. Nineteen patients (11.2%) had a best overall response of CR/PR (confirmed and unconfirmed). The DCR (CR + PR + SD ≥ 12 weeks) was 32% (54 of 169 patients). Programmed cell death ligand 1 status (based on MedImmune assay) was known for 143 of 169 evaluable patients, of whom 30 were PD-L1 positive (≥25% of tumour cells with membrane staining for PD-L1). A best overall response of CR/PR (confirmed and unconfirmed) was observed in 7 of 30 (23.3%) PD-L1-positive patients and in 6 of 113 (5.3%) PD-L1-negative patients.

Efficacy data on the NSCLC patients in Study 1108, presented at ESMO 2014 (cut-off date of 21 August 2014), showed a disease control rate at 12 weeks of 41% and ORR of 16% among 162 evaluable patients, with activity observed in both squamous and non-squamous histologies. The ORR was higher in patients with PD-L1 positive tumours (25%; 12 CR/PR; n=48) compared to patients with PD-L1 negative tumours (10%; 7 CR/PR; n=74) (Antonia et al 2014). More recent data has been presented at international oncology conferences (Rizvi et al 2015 ASCO). Please refer to latest MEDI4736 IB for complete details of efficacy of MEDI4736 across all clinical programs.

AstraZeneca data on file indicate that the best predictor of response using the PD-L1 assay is tumour membrane expression and that the current cut-off of 25% tumour cell staining effectively enriches for responders in the PD-L1-positive group. A subpopulation of patients within the positive group possessed tumour tissue samples characterised by ≥90% of tumour cells scoring membrane-positive for PD-L1. This group appeared to have a high likelihood of response (ORR ~39%; 7 CR/PR; n=18).

Therefore the potential benefit of enriching the patient population further by identifying patients whose NSCLC tumours are PD-L1 positive at or above the 90% threshold will be assessed in Cohort 3 of this study. This will assess the efficacy of MEDI4736 treatment in terms of ORR in patients with *EGFR/ALK* (anaplastic lymphoma kinase) wild type locally advanced/metastatic NSCLC whose tumour tissue samples have ≥90% of tumour cells with membrane staining for PD-L1 and who have received at least 2 prior systemic treatment regimens including a platinum-based chemotherapy regimen.

In view of the potential for MEDI4736 to have anti-tumour activity in the PD-L1 positive NSCLC population, the risk-benefit assessment favours the proposed 3 cohort study. All patients will be closely monitored and are able to stop treatment at any time if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for delaying an infusion or permanently stopping MEDI4736 are provided.

As the diagnostic to determine PD-L1 status was not available when the study first started there will be a number of patients in Cohorts 1 and 2 with tumours determined to be PD-L1 negative and positive (and possibly unknown) (based retrospectively on the patient's pre-treatment tumour sample). All patients, regardless of tumour PD-L1 status, will continue to be treated with MEDI4736 per protocol.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| Cohort 1<br>To assess the efficacy of MEDI4736 treatment in terms of ORR in PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>Cohort 2<br>To assess the efficacy of MEDI4736 treatment in terms of ORR in PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>Cohort 3<br>To assess the efficacy of MEDI4736 treatment in terms of ORR in PD-L1 positive patients with ≥90% of tumour cells with membrane staining | ORR using Independent Central Review assessments according to RECIST 1.1[a,b] |

a The primary analysis of ORR will be based on programmatically derived ORR based upon Independent Central Review assessment. Sensitivity analyses of ORR will also be performed based on tumour information recorded in the clinical database by the investigator according to RECIST 1.1 and upon ORR based on Independent Central Review assessment according to RECIST 1.1 modified for confirmation of progression.

b Objective tumour response (complete response or partial response) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

ORR Objective response rate; PD-L1 Programmed death ligand 1; RECIST Response Evaluation Criteria In Solid Tumours.

## 2.2 Secondary objectives

| Secondary Objective: | Outcome Measure: |
|---|---|
| Cohort 1<br>To further assess the efficacy of MEDI4736 in terms of: DoR, DCR, TTR, PFS and OS in PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>Cohort 3<br>To further assess the efficacy of MEDI4736 in terms of: DoR, DCR, TTR, PFS and OS in PD-L1 positive patients with ≥90% of tumour cells with membrane staining | DoR using Independent Central Review assessments according to RECIST 1.1[a]<br>DCR using Independent Central Review assessments according to RECIST 1.1[a]<br>TTR using Independent Central Review assessments according to RECIST 1.1[a]<br>PFS using Independent Central Review assessments according to RECIST 1.1[a]<br>OS |
| Cohort 2<br>Key secondary objectives:<br>To assess the efficacy of MEDI4736 in terms of ORR in<br>• Non-squamous PD-L1 positive (≥25% of tumour cells with membrane staining) patients<br>• PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br>• Non-squamous PD-L1 positive patients with ≥90% of tumour cells with membrane staining | ORR using Independent Central Review assessments according to RECIST 1.1[a,b]<br>DoR using Independent Central Review according to RECIST 1.1[a]<br>DCR using Independent Central Review assessments according to RECIST 1.1[a]<br>TTR using Independent Central Review assessments according to RECIST 1.1[a]<br>PFS using Independent Central Review assessments according to RECIST 1.1[a] |

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| Other secondary objectives:<br>To further assess the efficacy of MEDI4736 in terms of: DoR, DCR, TTR, PFS and OS in<br>• PD-L1 positive patients (≥25% of tumour cells with membrane staining)<br>• Non-squamous PD-L1 positive (≥25% of tumour cells with membrane staining) patients<br>• PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br>• Non-squamous PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br>To assess the efficacy of MEDI4736 in<br>• PD-L1 negative patients (<25% of tumour cells with membrane staining)<br>• Non-squamous PD-L1 negative (<25% of tumour cells with membrane staining) patients<br>• PD-L1 unselected patients (combined population of PD-L1 positive, PD-L1 negative and PD-L1 unknown patients who were enrolled under the original protocol [ie, prior to the amendment to only enrol PD-L1 positive patients])<br>• Patients with <90% of tumour cells with PD-L1 membrane staining<br>• Non-squamous patients with <90% of tumour cells with PD-L1 membrane staining | OS |
| Cohorts 2 and 3<br>To assess the efficacy of MEDI4736 in a combined population of Cohorts 2 and 3 for:<br>• PD-L1 positive patients with ≥90% of tumour cells with membrane staining<br>• Non-squamous PD-L1 positive patients with ≥90% of tumour cells with membrane staining | ORR using Independent Central Review assessments according to RECIST 1.1<br>DoR using Independent Central Review assessments according to RECIST 1.1<br>DCR using Independent Central Review assessments according to RECIST 1.1<br>TTR using Independent Central Review assessments according to RECIST 1.1<br>PFS using Independent Central Review assessments according to RECIST 1.1<br>OS |
| All cohorts<br>To assess the safety and tolerability profile of MEDI4736 | AEs, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, haematology and urinalysis |
| All cohorts<br>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) |

| Secondary Objective: | Outcome Measure: |
|---|---|
| All cohorts<br>To investigate the immunogenicity of MEDI4736 | ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed]) |

a Analysis of ORR, DoR, DCR, TTR and PFS and will be based upon Independent Central Review assessment. For the analyses to be conducted, see Sections 12.2.1, 12.2.2, 12.2.3, 12.2.4 and 12.2.5.
b Objective tumour response (complete response or partial response) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

ADA Anti-drug antibody; AE Adverse event; DCR Disease control rate; DoR Duration of response; ORR Objective response rate; OS Overall survival; PD-L1 Programmed death ligand 1; PFS Progression free survival; PK Pharmacokinetic(s); RECIST Response Evaluation Criteria In Solid Tumours; TTR Time to response.

## 2.3 Exploratory objectives

| Exploratory Objective: | Outcome Measure: |
|---|---|
| To explore immune-related response criteria as an assessment methodology for clinical benefit of MEDI4736 by Independent Central Review | ORR, DoR, DCR, TTR and PFS using Independent Central Review assessments according to immune-related response criteria |
| 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 collect blood and tissue samples for analysis of biomarkers including but 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 | Biomarker analysis of blood and tissue to assess exploratory markers including 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 before and after treatment with MEDI4736 and MEDI4736 PK exposure, clinical outcomes, efficacy, AEs and/or safety parameters | 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 treatments and/or susceptibility to disease (optional) | Correlation of polymorphisms with variation in PK, pharmacodynamics, safety or response parameters observed in patients treated with MEDI4736 and/or susceptibility to disease |
| To assess the efficacy in PD-L1 negative patients (where negative is defined as <25% of tumour cells with membrane staining) in Cohort 1 (if there are sufficient patients) and, additionally, in all patients in a combined population of Cohorts 1 and 2 | ORR, DoR PFS (using Independent Central Review assessments according to RECIST 1.1) and OS |

AE Adverse event; DCR Disease Control Rate; DoR Duration of response; IFN Interferon; IL Interleukin; ORR Objective response rate; OS Overall survival; PD-L1 Programmed death ligand 1; PFS Progression free survival; PK Pharmacokinetic(s); T-cell T lymphocytes; TTR Time to response.

Exploratory biomarker and PGx research will be reported outside the Clinical Study Report (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 II, non-comparative, open label, multi-centre study assessing the efficacy and safety of MEDI4736 in the treatment of male and female patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) that is PD-L1 positive who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen.

Patients will be enrolled in an *EGFR/ALK* cohort (positive or wild type) prior to the first infusion. Patients will be treated with MEDI4736 (10 mg/kg Q2W iv) for 12 months. There will be 3 cohorts:

- Cohort 1 will include patients who have EGFR tyrosine kinase (TK) mutations or ALK alterations (hereafter referred to as *EGFR/ALK* positive) and whose tumour tissue samples have ≥25% of tumour cells with membrane staining for PD-L1 (referred to as PD-L1 positive).

- Cohort 2 will include patients who do not have *EGFR* TK mutations or *ALK* alterations and patients whose *EGFR* TK mutation status or *ALK* fusion status is unknown (hereafter referred to as *EGFR/ALK* wild type) and whose tumour tissue samples have ≥25% of tumour cells with membrane staining for PD-L1 (referred to PD-L1 positive).

- Cohort 3, which will start recruiting once Cohort 2 has finished recruitment, will include patients who are *EGFR/ALK* wild type and whose tumour tissue samples have ≥90% of tumour cells with membrane staining for PD-L1.

The number of patients within Cohort 2 with ≥90% of tumour cells with membrane staining will not be known during recruitment. Each of the 3 cohorts will contain approximately 94 patients with tumours prospectively determined to be PD-L1 positive (as defined above). As the diagnostic to determine PD-L1 status was not available when the study first started there will be a number of patients in Cohorts 1 and 2 with tumours determined to be PD-L1 negative, PD-L1 positive or possibly unknown (based retrospectively on the patient's pre-treatment tumour sample). All patients, regardless of tumour PD-L1 status, will continue to be treated with MEDI4736 per protocol. The analysis of PD-L1 positive patients in

Cohorts 1 and 2 will include all patients, regardless of whether their PD-L1 status was determined prospectively or retrospectively.

Approximately 700 patients will be enrolled in Cohorts 1, 2 and another 700 patients in Cohort 3.

Approximately 700 patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) will be enrolled and undergo a pre-screening assessment on their tumour tissue sample to determine PD-L1 status (see Section 6.6.1). On the assumption that approximately 30% of patients from this population have tumours that are PD-L1 positive where positive is defined as ≥25% of tumour cells with membrane staining (proprietary PD-L1 immunohistochemistry assay; ) (AstraZeneca, unpublished data), it is anticipated that about 210 of the 700 pre-screened patients will have PD-L1 positive tumours and that 188 of these will go on to receive MEDI4736 in Cohorts 1 and 2 at 100 to 150 sites in North America, Asia, and Europe.

An additional group of patients with locally advanced or metastatic NSCLC will be enrolled and undergo a pre-screening assessment on their tumour tissue sample to identify patients who possess PD-L1 positive tumours with ≥90% of tumour cells with membrane staining (using the same proprietary assay). On the assumption that approximately 15% of patients from the advanced/metastatic NSCLC population have tumours that meet this threshold of PD-L1 staining (AstraZeneca, unpublished data), it is anticipated that, additionally, about 105 of 700 pre-screened patients will have ≥90% of tumour cells with membrane staining and that 94 of these will go on to receive MEDI4736 in Cohort 3.

The diagnostic and the decision to use the ≥25% cut-point to determine PD-L1 status in Cohorts 1 and 2 of this study was developed using external data (eg from Study 1108). Additionally, PD-L1 testing in this study has been completed only after the diagnostic – including the selected 25% threshold - was made available by Results generated to date have not retrospectively influenced this 25% cut-point selection. Similarly, the decision to use the additional ≥90% cut-point in Cohort 3 was based upon data external to this study (Study 1108).

All patients entering the study should have known *EGFR* TK mutation or *ALK* fusion status; however, in the event that no valid test result is available, eligible patients with unknown *EGFR* TK mutation or *ALK* fusion status will be enrolled into the *EGFR/ALK* wild type cohort that is open for enrolment at that time (recruitment to Cohort 3 will not commence until recruitment to Cohort 2 has been completed).

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

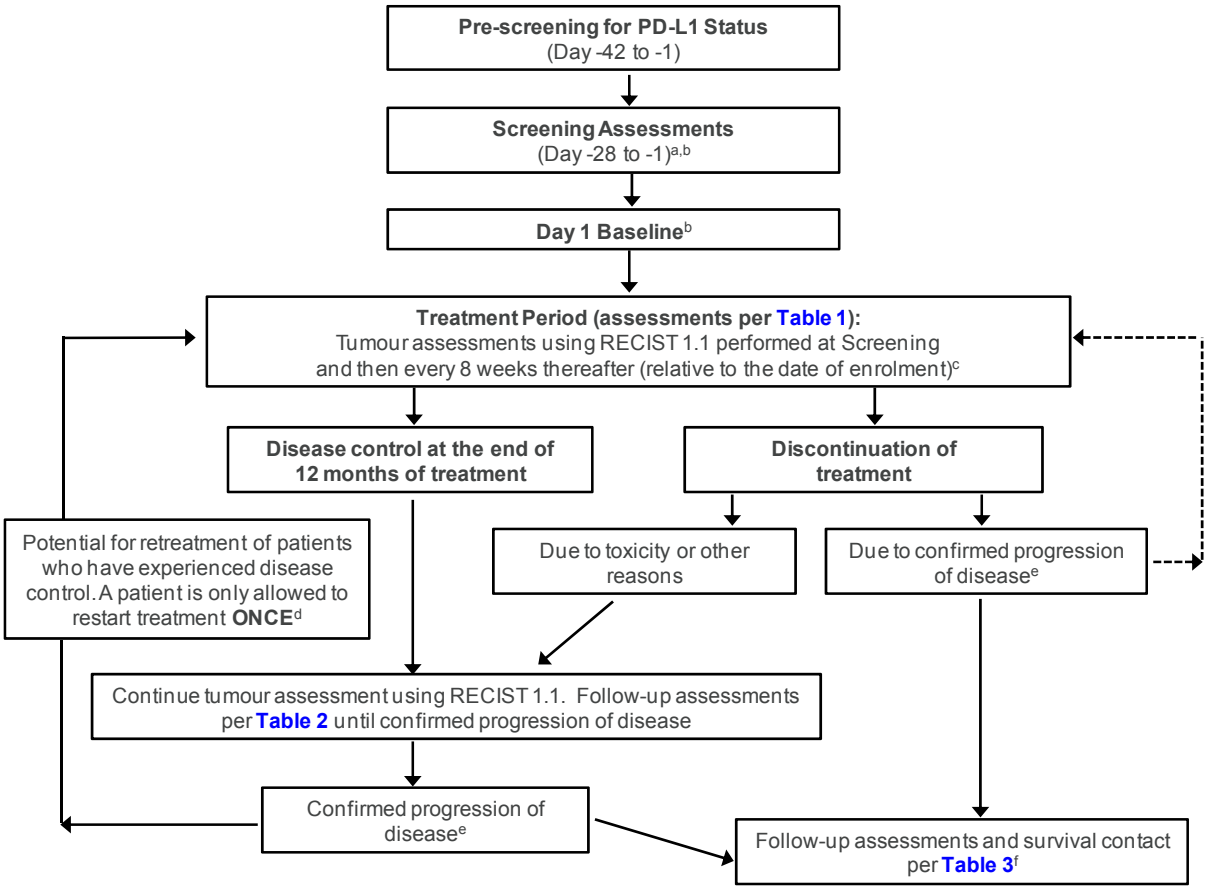
Patients receiving MEDI4736 will commence treatment on Day 1 and continue on a Q2W schedule for a maximum of 12 months. Treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. Patients who have discontinued treatment due to toxicity, symptomatic deterioration or who have commenced subsequent anti-cancer therapy will be followed up until confirmed disease progression or death (whichever occurs first).

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 as given by the Independent Central Review (ICR) will be used to derive the primary variable of ORR and secondary variables of DoR, TTR, PFS and DCR. Sensitivity analyses from ICR (according to RECIST modified for confirmation of progression and irRECIST 1.1) and from RECIST 1.1 measurements per the site investigator will also be performed. See Section 6.3 and Appendix F for further information regarding RECIST tumour assessments in this study.

For each cohort, the data cut-off for the analysis of ORR will take place approximately 24 weeks after the last patient is enrolled into each cohort. The data cut-off for the final analysis of OS (secondary endpoint) will take place approximately 12 months after the last patient is enrolled into each cohort.

The study flow chart is presented in Figure 1. 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 MEDI4736 treatment and achieved disease control (until confirmed PD) and patients who have discontinued MEDI4736 due to toxicity in the absence of confirmed PD is presented in Table 2. The schedule of study procedures during follow-up for patients who have discontinued MEDI4736 treatment due to confirmed PD is presented in Table 3. 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.

## Figure 1 Study flow chart




a Screening assessments can be performed in a step-wise process.

b Prior to treatment, patients will be enrolled in an *EGFR/ALK* cohort (positive or wild type).

c Objective tumour response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed. Disease progression also 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. Treatment with MEDI4736 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 still meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3 for this study including re-consenting to treatment.

d Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month MEDI4736 treatment period may restart MEDI4736 treatment upon evidence of PD, with or without confirmation, during follow-up. Before restarting treatment, the investigator should ensure patients still meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3 for this study including re-consenting to treatment. To restart treatment the patient must not have received an intervening systemic anti-cancer therapy post-MEDI4736 discontinuation. Patients should have a baseline tumour assessment within 28 days of restarting treatment with MEDI4736, all further scans should occur every 8 weeks (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

e Patients with confirmed PD that continue to receive MEDI4736 at the discretion of the investigator (following consultation with the sponsor) can receive treatment for a maximum of 12 months. For all patients who are treated through progression, the investigator should ensure patients still meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3 for this study including re-consenting to treatment. Patients will follow the assessments in Table 1 including tumour assessments every 8 weeks (relative to the date of the first infusion) until study treatment is stopped. Study drug should be discontinued if there is confirmed PD following a previous response (PR or CR) to study drug.

f Patients with confirmed PD that discontinue MEDI4736, should have scans conducted according to local practice and submitted for Independent Central Review until the patient commences a new treatment (these scans are optional).

Note: The DCO for the final analysis of overall survival will take place 12 months after the last patient is enrolled in each cohort. At this time point, patients who are receiving treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit, patients may continue to receive investigational product. For patients who do continue to receive treatment beyond the time of the final DCO, investigators will only continue to report all SAEs to Patient Safety until 90 days after investigational product is discontinued and any SAE or non-serious AE that is ongoing at the time of this DCO must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

AE Adverse event; ALK Anaplastic lymphoma kinase; CR Complete response; DCO Data cut-off; EGFR Epidermal growth factor receptor; ORR Objective response rate; 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 (12 months: maximum of 26 doses, last dose Week 50)**

| **Visit** (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.) | **Pre-screening for PD-L1 status ONLY** | **Screening** | **All assessments to be performed pre-infusion unless stated otherwise** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | **Every 2 weeks** | **Every 4 weeks** | **Every 8 Weeks** | **Every 12 weeks** |
| **Day** | **-42 to -1** | **-28 to -1** | **1** | **15** | **29** | **43** | **57** | **Day 1 of the week** | | | |
| **Week** | **-6 to -1** | **-4 to -1** | **0** | **2** | **4** | **6** | **8** | **10, 12, 14, 16 etc** | **12, 16, 20, 24, 28, etc** | **16, 24, 32, 40 and 48** | **16, 28, 40, 52** |
| | | | | **(±3 days)** | | | | | | **(±7 days)** | |
| Written informed consent/assignment of patient identification number | X | | | | | | | | | | |
| Preliminary eligibility fulfilment (investigator's opinion) | X | | | | | | | | | | |
| Demography and history of tobacco and alcohol use[a] | X | | | | | | | | | | |
| Previous treatments for NSCLC | X | | | | | | | | | | |
| Archival FFPE tumour tissue sample for PD-L1 assay (Section 6.6)[a] | X | | | | | | | | | | |
| Recent formalin-fixed tumour biopsy for PD-L1 assay (Section 6.6)[a] | X | | | | | | | | | | |
| Formal verification of eligibility criteria | | X | X | | | | | | | | |
| Medical and surgical history | | X | | | | | | | | | |
| Hepatitis B and C; HIV | | X | | | | | | | | | |
| Urine hCG or serum βhCG | | X | X | X | X | X | X | X | | | |
| Kit assignment and MEDI4736 administration | | | X | X | X | X | X | X | | | |
| Physical examination | 권X | X | X | X | X | X | X | | X | | |
| Vital signs (pre- and post-infusion vital signs assessments; Section 6.4.8) | | X | X | X | X | X | X | X | | | |
| Weight | | X | X | | X | | X | | X | | |
| Electrocardiogram | | X | X[b] | | | | X | | | X[b] | |

**Table 1 Schedule of study procedures: Screening and Treatment Period (12 months: maximum of 26 doses, last dose Week 50)**

| **Visit** (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.) | **Pre-screening for PD-L1 status ONLY** | **Screening** | **All assessments to be performed pre-infusion unless stated otherwise** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | **Every 2 weeks** | **Every 4 weeks** | **Every 8 Weeks** | **Every 12 weeks** |
| **Day** | **-42 to -1** | **-28 to -1** | **1** | **15** | **29** | **43** | **57** | **Day 1 of the week** | | | |
| **Week** | **-6 to -1** | **-4 to -1** | **0** | **2** | **4** | **6** | **8** | **10, 12, 14, 16 etc** | **12, 16, 20, 24, 28, etc** | **16, 24, 32, 40 and 48** | **16, 28, 40, 52** |
| | | | | **(±3 days)** | | | | | | **(±7 days)** | |
| Adverse event/serious adverse event assessment | | X | X | X | X | X | X | X | | | |
| Concomitant medications | | X | X | X | X | X | X | X | | | |
| Palliative radiotherapy | | As clinically indicated (see Section 5.1) → | | | | | | | | | |
| World Health Organisation performance status | | X | X | X | X | X | X | X | | | |
| Serum chemistry[c] | | X | X | X | X | X | X | X | | | |
| Amylase, lipase (where available) | | X | X | | X | | X | | X | | |
| Thyroid function tests (TSH and T3 and T4) | | X | X | | X | | X | | X | | |
| Haematology[c] | | X | X | X | X | X | X | X | | | |
| Urinalysis[d] | | X | X | | X | | X | | X | | |
| Coagulation parameters[e] | | X | | | | | | | | | |
| Pharmacokinetic assessment[a] | | | X (and EOI) | | X | | | | | | X[f] |
| Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in patient circulation) [a] | | | X | | X | | | | | | X[f] |
| sPD-L1 concentration (to assess target engagement) [a] | | | X | | | | | | | | X[g] |
| Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumour and self antigens in circulation) | | | X | | X | | | | X (Week 12 only) | | |

## Table 1 Schedule of study procedures: Screening and Treatment Period (12 months: maximum of 26 doses, last dose Week 50)

| Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.) | Pre-screening for PD-L1 status ONLY | Screening | All assessments to be performed pre-infusion unless stated otherwise | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Every 2 weeks | Every 4 weeks | Every 8 Weeks | Every 12 weeks |
| **Day** | -42 to -1 | -28 to -1 | 1 | 15 | 29 | 43 | 57 | Day 1 of the week | | | |
| **Week** | -6 to -1 | -4 to -1 | 0 | 2 | 4 | 6 | 8 | 10, 12, 14, 16 etc | 12, 16, 20, 24, 28, etc | 16, 24, 32, 40 and 48 | 16, 28, 40, 52 |
| | | | | (±3 days) | | | | | | (±7 days) | |
| miRNA/mRNA (to examine immune cell gene expression profiles in circulation) | | | X | | | | X | | | X (Week 48 only) | |
| PGx sample (optional [DNA element])[a] | | X | | | | | | | | | |
| Tumour assessment (CT or MRI)[h,i,j] | | X | | | | | X | | | X | |

a Assessment will not be repeated if patient is re-treated.
b On Day 1 and Week 16, ECGs should be taken within an hour prior to the start of the infusion, within 30 minutes post-infusion, and 3 hours (±15 minutes) post-infusion.
c If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for urea and electrolytes, full blood count and liver function tests must be available before commencing an infusion. Gamma-glutamyl transferase 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.
d Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.
e Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.
f These assessments will be performed every 12 weeks following the Week 4 assessment; thus at Week 16, Week 28, etc.
g sPD-L1 concentration will be performed at Day 1 and Week 16 of the treatment period only.
h RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy may be imaged based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed every 8 weeks for the first 48 weeks (relative to the date of the first infusion of MEDI4736) until confirmed objective disease progression per RECIST 1.1. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of the first infusion) and no less than 4 weeks after the initial assessment of CR/PR and PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of the first infusion). All confirmatory scans should be recorded on the database. 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, and that the patient still fulfils eligibility criteria for this study including re-consenting to continue treatment. The patient must still meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study treatment.

i Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month MEDI4736 treatment period may restart treatment with MEDI4736 upon evidence of PD, with or without confirmation, during follow-up. Before restarting MEDI4736, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient, and that the patient still fulfils eligibility criteria for this study including re-consenting to restart MEDI4736. To restart treatment the patient must not have received an intervening systemic anti-cancer therapy post-MEDI4736 discontinuation. Patients should have a baseline tumour assessment within 28 days of restarting treatment with MEDI4736, all further scans should occur every 8 weeks (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

j Patients with confirmed PD who continue to receive MEDI4736 at the discretion of the investigator can receive treatment for a maximum of 12 months. Patients will have scans every 8 weeks while on treatment (relative to the date of the first infusion) until study treatment is stopped. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study treatment. Study drug should be discontinued if there is confirmed PD following a previous response (PR or CR) to study drug.

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

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

Note: For ‘re-treatment’ patients who go onto have a subsequent 12 months of treatment the same assessments should be done as in the screening and the first 12 month treatment period with the exception of the PK, ADA, sPD-L1, PGx and biopsy assessments which do not need to be collected a second time.

**Table 2 Schedule of study procedures: follow-up for patients who have completed MEDI4736 treatment and achieved disease control (until confirmed progression of disease) and patients who have discontinued MEDI4736 due to toxicity in the absence of confirmed progression of disease**

| Evaluation | Time Since Last Dose of MEDI4736 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months (±2 weeks) |
| | 30 | 2 | 3 | 4 | 6 | 8 | 10 | |
| Physical examination | X | | | | | | | |
| Vital signs (temperature, respiratory rate, blood pressure, pulse, oxygen saturation; see Section 6.4.8) | X | | | | | | | |
| Weight | X | | | | | | | |
| Electrocardiogram | X | | | | | | | |
| AE/SAE assessment | X | X | X | | | | | |
| Concomitant medications | X | | | | | | | |
| Palliative radiotherapy | As clinically indicated (see Section 5.1) → | | | | | | | |
| World Health Organisation performance status | X | | X | | | | | |
| Subsequent anti-cancer therapy | X | X | X | X | X | X | X | X |
| Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted | | X | X | X | X | X | X | X (every 2 months) |
| Haematology | X | X | 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[a] | As clinically indicated → | | | | | | | |
| Urinalysis | As clinically indicated → | | | | | | | |
| Pharmacokinetic assessment | | | X | | | | | |

**Table 2 Schedule of study procedures: follow-up for patients who have completed MEDI4736 treatment and achieved disease control (until confirmed progression of disease) and patients who have discontinued MEDI4736 due to toxicity in the absence of confirmed progression of disease**

| Evaluation | Time Since Last Dose of MEDI4736 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months (±2 weeks) |
| | 30 | 2 | 3 | 4 | 6 | 8 | 10 | |
| 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 | | | | | | | |
| Tumour assessment (CT or MRI)[b] | For patients who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 12 weeks relative to the date of **first infusion** thereafter 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 MEDI4736 due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the relative to the date of **first infusion** as follows: every 8 weeks for the first 48 weeks (per Table 1), then every 12 weeks 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 Coagulation tests: prothrombin time, APTT and INR will be performed if clinically indicated.
b RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy may be imaged based on signs and symptoms of individual patients.

ADA Anti-drug antibody; AE Adverse event; APTT Activated partial thromboplastin time; CR Complete response; CT Computed tomography; INR International normalised ratio; miRNA Micro ribonucleic acid; MRI Magnetic resonance imaging; mRNA Messenger ribonucleic acid; PD Progression of disease; PR Partial response; 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 MEDI4736 treatment due to confirmed progression of disease**

| Evaluation | Time Since Last Dose of MEDI4736 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months (±2 weeks) |
| | 30 | 2 | 3 | 4 | 6 | 8 | 10 | |
| Physical examination | X | | | | | | | |
| Vital signs (temperature, respiratory rate, blood pressure, pulse, oxygen saturation; see Section 6.4.8) | X | | | | | | | |
| Weight | X | | | | | | | |
| Electrocardiogram | X | | | | | | | |
| AE/SAE assessment | X | X | X | | | | | |
| Concomitant medications | X | X | X | | | | | |
| Palliative radiotherapy | As clinically indicated (see Section 5.1) → | | | | | | | |
| World Health Organisation performance status | X | | | | | | | |
| Subsequent anti-cancer therapy | X | X | X | X | X | X | X | X |
| Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted | | X | X | X | X | X | X | X (every 2 months) |
| Haematology | X | X | X | | | | | |
| Serum chemistry | X | X | X | | | | | |
| Amylase, lipase (where available) | X | X | X | | | | | |
| Thyroid function tests (TSH, and T3 and T4) | X | | | | | | | |
| Coagulation parameters[a] | As clinically indicated → | | | | | | | |
| Urinalysis | As clinically indicated → | | | | | | | |
| Pharmacokinetic assessment | | | X | | | | | |

**Table 3 Schedule of study procedures: follow-up for patients who have discontinued MEDI4736 treatment due to confirmed progression of disease**

| Evaluation | Time Since Last Dose of MEDI4736 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Day (±3) | Months (±1 week) | | | | | | 12 Months and Every 6 Months (±2 weeks) |
| | 30 | 2 | 3 | 4 | 6 | 8 | 10 | |
| 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 | | | | | | | |
| Tumour assessment (CT or MRI)[b] | For patients who **continue on MEDI4736 post-confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of **first infusion** per Table 1 until MEDI4736 is stopped.<br>For patients who **discontinue MEDI4736 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 Coagulation tests: prothrombin time, APTT and INR will be performed if clinically indicated.
b Study drug should be discontinued if there is confirmed PD following a previous response (PR or CR) to study drug.
ADA Anti-drug antibody; AE Adverse event; APTT Activated partial thromboplastin time; CT Computed tomography; INR International normalised ratio; miRNA Micro ribonucleic acid; MRI Magnetic resonance imaging; mRNA Messenger ribonucleic acid; 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

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

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

The single-arm study design will enable rapid recruitment and the study will be used as part of the registration package for MEDI4736 aimed at a patient population with significant clinical unmet need.

Although clinical experience with MEDI4736 is limited, currently available data from the MEDI4736 FTIH study (Section 1.1.3.2 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 advanced NSCLC who have failed multiple lines of therapy.

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 have a high probability of ensuring a response in the majority of patients.

This recommendation is supported by multiple lines of evidence including: in-vitro data, nonclinical activity, clinical PK-pharmacodynamics, 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. Pharmacokinetic parameters such as dose-normalised area under the plasma 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%), pharmacodynamic 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. Of the 220 patients who received MEDI4736 monotherapy and for whom PK/ADA data were available as of July 2014, 5 were detected to be ADA positive, with an impact on PK/pharmacodynamics reported in 1 patient. Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 10 mg/kg Q2W.

The patient population in this single arm study will be split into 3 cohorts based on patients' *EGFR* TK mutation and *ALK* fusion status and also tumour PD-L1 expression. The primary rationale for this is that there are clear biological and treatment outcome differences between patients with NSCLC with *EGFR/ALK* positive tumours and those patients with *EGFR/ALK* wild type/unknown tumour status. It is considered that patients with "actionable mutations", which have subsequently received the appropriate molecularly targeted therapy (ie, EGFR or ALK TKI) as part of their prior courses of treatment, comprise a subgroup of NSCLC patients with a different clinical course and prognosis distinct from those with proven *EGFR/ALK* wild type status. Therefore, assessing efficacy and safety separately in patients with mutant or *EGFR/ALK* wild type/unknown tumours is a reasonable choice based on the natural history of the disease and response to therapy, which ultimately impacts prognosis and OS. This rationale also supports the inclusion of eligible patients with unknown *EGFR* TK mutation or ALK fusion status in the *EGFR/ALK* wild type cohort; in the event that no valid test result is available. Collection of appropriate tissue samples to enable retrospective confirmation/classification of patients according to their *EGFR* mutation or ALK fusion status will ensure greater confidence in our ability to understand MEDI4736 activity in each patient type.

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

and 33% having PRs. In contrast, in patients with PD-L1 negative tumours, they found only a 13% ORR with 28% of patients having SD and 13% having PRs. Similarly, in data presented at the Annual Meeting of the American Society of Clinical Oncology 2013 by Bristol-Myers Squibb (Grosso et al 2013), PD-L1 staining when assessed using a different method and scoring algorithm appeared to be associated with greater clinical benefit in patients with metastatic melanoma treated with nivolumab (anti-PD-1). They found a 44% ORR in patients with PD-L1 positive tumours versus a 17% ORR in patients with PD-L1 negative tumours. Additionally, in their studies, patients with tumours that were PD-L1 positive had a higher PFS (9.1 versus 2.0 months) and OS than patients with PD-L1 negative tumours (21 versus 12 months). Also, in a data set presented by Merck & Co at the World Conference on Lung Cancer (Garon et al 2013), analysis of the relationship between PD-L1 expression status and response rates in a cohort of patients with NSCLC indicated that tumour samples displaying high levels of expression (according to their assay criteria) were associated with response rates of 67% (6/9) per irRC and 57% (4/7) per RECIST. In contrast, tumour samples expressing zero/low levels of PD-L1 were associated with response rates of 4% (1/24) per irRC and 9% (2/22) per RECIST.

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

AstraZeneca data on file indicate that the best predictor of response using the PD-L1 assay is tumour membrane expression and that the current cut-off of 25% tumour cell staining effectively enriches for responders in the PD-L1-positive group. A subpopulation of patients within the positive group possessed tumour tissue samples characterised by ≥90% of tumour cells scoring membrane-positive for PD-L1. This group appeared to have a high likelihood of response (ORR ~39%; 7 CR/PR; n=18). Therefore the potential benefit of enriching the patient population further by identifying patients whose NSCLC tumours are PD-L1 positive at or above the 90% threshold will be assessed in Cohort 3 of this study.

Given that tumours evolve with time and in response to treatment, archived samples of tumour tissue may not accurately reflect the current state of disease due to the time intervals that may occur between diagnostic sample collection and late-line treatment. Therefore, archived samples will be collected as well as a recent (≤3 months) tumour biopsy (taken following completion of the most recent therapy) to ascertain the PD-L1 status and to gain understanding about the relationship between these samples in determining which sample type may have the greatest utility for informing us about patients.

The primary aim of this study is to determine the efficacy of MEDI4736 (10 mg/kg Q2W via iv infusion) in terms of ORR. ORR can be a useful endpoint in single arm studies because it is a direct measure of the drug's anti-tumour activity (Pazdur 2008). The use of ORR in the third/fourth-line setting, especially when the responses are sustained and durable (a key

feature of immunotherapy), is justified because it is anticipated that it will serve as an early measure of clinical benefit that may be confirmed by the survival endpoint employed in a planned randomised confirmatory study. The kinetics of anti-PD-L1 response also favour the use of ORR as a potential surrogate endpoint because response occurs from the first 6 weeks of treatment (earlier than other immunotherapeutic agents such as anti-CTLA-4) (Brahmer et al 2012, Spigel et al 2013). In patients treated with immunotherapies, including MEDI4736, relapse after response can be uncommon; reinforcing the importance of ORR as a likely surrogate for clinical benefit.

Anti-tumour activity will be assessed according to RECIST v1.1 guidelines. The primary analysis will be based on the programmatically-derived ORR based on ICR assessments using RECIST, and using all scans regardless of whether they were scheduled or not. Sensitivity analyses of ORR from the site investigator tumour data will also be performed according to RECIST 1.1 and additionally from the ICR according to RECIST, modified for confirmation of progression and irRECIST 1.1 (see Section 11.2).

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

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

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, eg, European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anti-cancer compounds, the study implements the following:

- 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. Treatment with MEDI4736 will continue between the initial assessment of progression and confirmation for progression.

- In addition, patients may continue to receive MEDI4736 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 MEDI4736 and provide a more complete evaluation of its anti-tumour activity than would be seen with conventional response criteria. Nonetheless, the primary analysis of each efficacy endpoint will be conducted 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).

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 retreatment with immune-mediated therapy. Responses with immune-mediated therapy are no different than responses to initial treatment in terms of time to response, DoR, or maintenance of response beyond treatment discontinuation (Hodi et al 2010, Forde et al 2014).

Therefore, patients who achieve and maintain disease control (ie, complete response [CR], PR or SD) through to the end of the 12-month MEDI4736 treatment period may also restart treatment with MEDI4736 upon evidence of disease progression during follow-up (maximum of 12 months of further treatment).

The patient must **not have** received an intervening systemic anti-cancer therapy after discontinuing MEDI4736 and should have a baseline tumour assessment within 28 days of restarting treatment with MEDI4736 (see Table 1).

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]).

# 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 EITHER

- Histologically- or cytologically-documented NSCLC who present with Stage IIIB/ Stage IV 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]), OR

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

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

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

- Patients with tumours with activating *EGFR* TK mutations must have received an EGFR TKI and patients with tumours that are *ALK* fusion positive must have received an ALK TKI, given before or after the platinum-based chemotherapy regimen

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

- Prior platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease is considered first-line therapy only if

recurrent (local or metastatic) disease developed within 6 months of completing therapy. Patients with recurrent disease >6 months must also have progressed after a subsequent platinum-based chemotherapy regimen given to treat the recurrence.

6. Patient's tumour sample must be PD-L1 positive (≥25% of tumour cells with membrane staining [Cohorts 1 and 2]) or PD-L1 positive with ≥90% of tumour cells with membrane staining (Cohort 3): either recent or archival sample) based on central assessment. Sample requirements as follows:

- A mandatory provision of a recent (≤3 months) tumour biopsy taken following the completion of the most recent systemic anti-cancer therapy, except if technically not feasible and after discussion with the study physician (for collection and processing procedures, refer to Section 6.6.1 and the Laboratory Manual). Tumour lesions planned for biopsy must not be used as index lesions for assessment of disease
AND

- 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 6.6.1 and the Laboratory Manual for details).

Additional biopsies may be performed to test for PD-L1 status at the Investigator's discretion.

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

8. Life expectancy ≥12 weeks at Day 1

9. World Health Organisation (WHO) Performance Status of 0 or 1

10. Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered 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).

11. 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.
- In patients with no liver metastasis: AST and ALT ≤2.5 x ULN
- In patients with liver metastasis: AST or ALT ≤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 treatment in a previous durvalumab (MEDI4736) clinical study

3. Participation in another clinical study with an investigational product during the last 4 weeks

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

5. Mixed small cell and NSCLC histology

6. Receipt of any investigational drug within 4 weeks prior to the first dose of MEDI4736

7. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolisation, monoclonal antibodies) ≤21 days prior to the first dose of MEDI4736 (≤14 days prior to the first dose of MEDI4736 for patients who have received prior TKIs [eg, erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C). If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca/MedImmune and the investigator.

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

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

10. 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.

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

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

13. Receipt of radiation therapy within 4 weeks prior to starting MEDI4736. Limited field of radiation for palliation within 2 weeks of the first dose of study treatment is allowed, provided:

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

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

15. 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.

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

17. History of primary immunodeficiency

18. History of allogeneic organ transplant

19. History of hypersensitivity to MEDI4736 or any excipient

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

21. History of leptomeningeal carcinomatosis

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

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

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

25. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving MEDI4736

26. 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.

27. 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.

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

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

**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 Retreatment

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

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

For all patients who are treated through progression, 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. Patients who progressed during the first 12 months are not allowed re-treatment. In addition, the investigator should ensure patients meet the following inclusion criteria (criteria number from section 4.1):

- The patient must provide signed, written and dated retreatment or treatment through progression informed consent (criterion 1). 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 11) and the criterion for AST/ALT.

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

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

- Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid (criterion 8)

- 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 10)

- Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1 (criterion 11)

- 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) (criterion 12)

- Recent major surgery within 4 weeks prior to entry to retreatment (excluding the placement of vascular access) that would prevent administration of investigational product (criterion 14)

- 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 15)
- Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis) (criterion 16)
- History of primary immunodeficiency (criterion 17)
- History of allogeneic organ transplant (criterion 18)
- History of hypersensitivity to MEDI4736 or any excipient (criterion 19)
- Brain metastases or spinal cord compression unless asymptomatic, treated and stable off steroids and anti-convulsants for at least 1 month prior to entry to retreatment (criterion 20)
- History of leptomeningeal carcinomatosis (criterion 21)
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction (criterion 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 (criterion 23)
- Active infection of tuberculosis, as determined by clinical signs and symptoms (criterion 24)
- Receipt of live attenuated vaccination within 30 days prior to retreatment or within 30 days of receiving MEDI4736 (criterion 25)
- 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 27)
- 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 28)

# 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 investigational product; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

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

   - Patients must use 2 acceptable methods of effective contraception as described in Table 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 investigational product.

**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

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

Restrictions relating to concomitant medications are described in Section 5.6.

## 5.2 Patient enrolment

At Pre-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.

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

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

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

At Screening, the Principal Investigator, or suitably trained delegate, will:

5. Determine formal patient eligibility (see Sections 4.1 and 4.2).

At Day 1 (Baseline), once the patient is confirmed to be eligible, the Principal Investigator, or suitably trained delegate, will:

6. Call IVRS/IWRS for kit assignment.

Patients may be enrolled but not treated. If the patient is not treated, the IVRS/IWRS should be contacted to terminate the patient in the system.

The IVRS/IWRS will be used to track drug supply.

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

All patients entering the study should have known *EGFR* TK mutation or *ALK* fusion status to ensure patients are assigned to the appropriate cohort. Recruitment into Cohort 3 will only start once recruitment into Cohort 2 is complete.

The study is designed to accrue at least 188 PD-L1 positive patients (94 patients with ≥25% of tumours with membrane staining for each of Cohorts 1 and 2) and, in addition, at least 94 PD-L1 positive patients with ≥90% of tumour cells with membrane staining for Cohort 3. However, due to the lag time associated with determination of PD-L1 status relative to dosing, there will be over-recruitment into any cohort.

In the event that no valid test result is available, eligible patients with unknown *EGFR* TK mutation or *ALK* fusion status will be enrolled into the *EGFR/ALK* wild type cohorts.

The IVRS/IWRS may not be available at the start of the study. In this event a manual process will need to be followed.

## 5.3 Procedures for handling patients incorrectly enrolled or initiated on investigational product

**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, or are incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion must occur between the study physician and the investigator regarding the patient's safety and well-being and whether to continue or discontinue the patient from the investigational product.

The study physician is to ensure all such contacts are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped, then enter follow-up where possible as per Section 5.8.

## 5.4 Blinding and procedures for unblinding the study

Not applicable; this is an open label study.

## 5.5 Treatments

### 5.5.1 Identity of investigational product(s)

#### 5.5.1.1 MEDI4736

The Investigational Products Supply section of AstraZeneca/MedImmune will supply MEDI4736 to the investigator as a lyophilised powder for reconstitution.

| 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 |

#### 5.5.1.2 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 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 10 mg/kg via iv infusion Q2W ±3 days. Treatment with MEDI4736 will commence on Day 1 following confirmation of eligibility and will

continue on a Q2W schedule for a maximum duration of treatment of 12 months (see Table 1). The final administration of MEDI4736 will be at the Week 50 visit. Treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur.

Disease progression requires confirmation, treatment with MEDI4736 will continue between the initial assessment of progression and confirmation for progression.

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

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month MEDI4736 treatment period will enter follow-up (Table 2). Upon evidence of PD following discontinuation of 12 months of treatment, patients may restart treatment with MEDI4736 for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period (Table 1). Patients will only be able to restart treatment once; thus a maximum of two 12-month periods will be allowed.

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 in the 12-month period after restarting MEDI4736 and cannot continue to receive MEDI4736 will enter follow-up with assessments as shown in Table 3.

Patients with PD that continue to receive MEDI4736 at the discretion of the investigator (following consultation with the sponsor) can receive treatment for a maximum of 12 months (and will follow the assessments in Table 1 including tumour assessments).

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

#### 5.5.2.1 **MEDI4736 treatment administration**

Following preparation of MEDI4736 (see Section 5.5.1.2), 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 MEDI4736 solution should not be infused through an iv line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of MEDI4736 administration must be recorded in the source documents.

#### 5.5.2.2 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in Section 6.4.8.1.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of MEDI4736 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. If, following 4 hours of interruption, there is persistent Grade 2 toxicity despite the use of appropriate medications such as antihistamines or acetaminophen, then study treatment should then be discontinued. If, following 4 hours of interruption, there is a decrease to Grade 1, then the drug may be re-introduced if it does not present an increased risk to the subject. If the infusion-related reaction is ≥Grade 3 or higher in severity, treatment with MEDI4736 will be discontinued.

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

### 5.5.3 Management of toxicity

The guidance that should be followed for management of toxicities is presented in the MEDI4736 toxicity management plan in Appendix G. 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.

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

2. If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of MEDI4736 along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for MEDI4736 (see the MEDI4736 toxicity management plan in Appendix G).

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

In addition, there are certain circumstances in which MEDI4736 should be permanently discontinued (see Section 5.8 and Appendix G).

Following the first dose of MEDI4736, subsequent administration of MEDI4736 can be modified based on toxicities observed as described in Appendix G. All toxicities will be graded according to CTCAE Version 4.03. Dose reductions are not permitted.

Dose modifications will not be required for AEs that are clearly not attributed to MEDI4736 (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 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 characterise and understand them in association with the use of this investigational product.

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

**MEDI4736 adverse events of special interest**

Adverse events of special interest 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 immune-related adverse event (irAE) is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an 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, but are not limited to:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (ie, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (ie, events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis

- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the MEDI4736 Investigator Brochure.

### 5.5.4 Additional study drug

No additional study drug is required in this study.

### 5.5.5 Labelling

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

The label will include the following information:

- Name of sponsor (AstraZeneca)
- Investigational product 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 investigational product is dispensed)
- The period of use eg, expiry date.
- Product Lot Identifier
- Medication Identity Number
- For clinical study use only
- Keep out of reach of children.

Labels will be provided as multi-language booklet labels with no tear off. For patients enrolled prior to the use of an IVRS, information relating to the administration of MEDI4736 will be captured in the patient's records.

### 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 anti-cancer therapy
- Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).
- 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 investigational product-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 MEDI4736 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 Clinical Research Associate will check these records to confirm the compliance with the protocol administration schedule.

Use of MEDI4736 in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 13.2 for procedures in case of overdose.

**Accountability**

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

The study personnel will account for all study drugs dispensed to and returned from the patient.

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

## 5.8 Discontinuation of investigational product

Patients must 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 investigational therapy might constitute a safety risk
- Any AE that meets criteria for discontinuation, as defined in Appendix G
- An AE related to MEDI4736 that is ≥Grade 3, with the exception of toxicities that do not meet criteria for discontinuation as defined in Appendix G
- ≥Grade 3 infusion reaction
- Initiation of alternative anti-cancer therapy including another investigational agent

- Confirmed PD and investigator determination that the patient is no longer benefiting from treatment with MEDI4736
- Confirmed PD following a previous response (PR or CR) to study drug
- Pregnancy or intent to become pregnant.

If the patient is discontinued from investigational product, 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.

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

**Procedures for discontinuation of a patient from investigational product**

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

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 all study drugs should be returned by the patient.

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

**Assessments following withdrawal of MEDI4736**

Patients who are permanently discontinued from receiving investigational product 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, 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. 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 in the absence of 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 MEDI4736 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 MEDI4736 treatment 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 treatment (confirmed PD or permanent withdrawal from the study).

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 MEDI4736 at the discretion of the investigator, who can receive treatment for a maximum of 12 months and will follow the assessments in Table 1 including tumour assessments until MEDI4736 is discontinued.

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 in the absence of confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]).

## 5.9 Withdrawal from study

Patients must 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 (including pre-screening) free to withdraw from the 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 all study drugs should be returned by the patient.

If consent is withdrawn, the patient will not receive any further investigational product 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 in the absence of 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 MEDI4736 treatment and achieved disease control (until confirmed PD) and patients who have discontinued MEDI4736 due to toxicity in the absence of confirmed PD is presented in Table 2. The schedule of study procedures during follow-up for patients who have discontinued MEDI4736 treatment due to confirmed PD is presented in Table 3.

## 6.1 Recording of data

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

The investigator ensures the accuracy, completeness, 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 dose of MEDI4736 (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
- Preliminary eligibility criteria (investigator's opinion)
- Demographic details including age, sex and ethnicity and also tobacco and alcohol consumption history
- Details on previous treatments for NSCLC
- A mandatory provision of a recent (≤3 months) tumour biopsy taken following the completion of the most recent systemic anti-cancer therapy, except if technically not feasible and after discussion with the study physician (for collection and processing procedures, refer to Section 6.6.1 and the Laboratory Manual). Tumour lesions planned for biopsy must not be used as index lesions for assessment of disease
  AND

- 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 6.6.1 and the Laboratory Manual for details).

The following assessments and procedures should be performed within 28 days prior to the first dose of MEDI4736 (Table 1). For details of the nature of the assessments, see below.

- Formal eligibility criteria verification
- Past medical and surgical history
- Details of any palliative radiotherapy
- Physical examination to assess all conditions that are current and ongoing
- Weight and vital signs: body temperature, respiratory rate, pulse, systolic and diastolic blood pressure (BP) 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
- 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
- Blood samples for the analysis of biomarkers (including those for circulating soluble factors, messenger RNA/micro RNA and soluble PD-L1; see Section 6.6).
- 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 and survival follow-up

Patients should be discontinued from MEDI4736 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 in the absence of confirmed PD) and Table 3 (for patients discontinuing due to confirmed PD).

Any serious and/or non-serious AEs ongoing at the time of treatment discontinuation or which have occurred during the follow-up period must be followed-up (in accordance with Section 6.4.3 and Section 6.4.4). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF.

**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 in the absence of confirmed PD) and Table 3 (patients discontinuing due to confirmed PD).

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 data cut-off for the final analysis of OS, which will take place 12 months after the last patient is enrolled in each cohort, 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.

## 6.3 Efficacy

### 6.3.1 Method of assessment using RECIST 1.1 criteria

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

The 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.

The baseline assessment should be performed no more than 28 days before the start of MEDI4736 treatment and ideally as close as possible to the start of investigational product. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks for the first 48 weeks (relative to the date of the first MEDI4736 infusion; Table 1), then every 12 weeks thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment/or subsequent therapy). If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

For patients who discontinue MEDI4736 due to toxicity in the absence of confirmed objective progression objective tumour assessments should be continued every 8 weeks for 48 weeks (relative to the date of the first MEDI4736 infusion) then every 12 weeks 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. Treatment with MEDI4736 will continue between the initial assessment of progression and confirmation for progression. For all patients who are treated through progression and for patients who achieve disease control (ie, CR, PR or SD) at 12 months and restart study treatment upon evidence of PD (according to RECIST 1.1), with or without confirmation, 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. The patient must continue to meet those inclusion and exclusion criteria including re-consenting to continue or restart 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)
- 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 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 confirmed objective disease progression.

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

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

If the investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify 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 are patients with

confirmed PD that continue to receive MEDI4736 at the discretion of the investigator (after consultation with the sponsor); these patients can receive treatment for a maximum of 12 months and will have scans every 8 weeks (relative to the date of the first infusion per Table 1) until study treatment is stopped.

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

Patients with confirmed PD that discontinue MEDI4736, should have scans conducted according to local practice and submitted for ICR until the patient commences a new treatment (these scans are optional; see Table 3).

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month MEDI4736 treatment period may restart treatment with MEDI4736 upon evidence of PD, with or without confirmation, during follow-up. To restart treatment the patient must not have received an intervening systemic anti-cancer therapy post-MEDI4736 discontinuation. Patients who restart MEDI4736 must have a baseline tumour assessment within 28 days of restarting treatment with MEDI4736, all further scans should occur every 8 weeks (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

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 in the absence of confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]) and Appendix F.

### 6.3.2 Central reading of scans

An ICR of all scans used in the assessment of tumours using RECIST 1.1 modified for confirmation of progression and irRC (Wolchok et al 2009, Nishino et al 2013, see Section 11.1.2) will be conducted (see Section 12.2.1 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.

### 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 investigational product).

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 investigational product).

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumour assessments using RECIST, drug or procedure-related

SAEs must be captured until the patient is considered to have confirmed PD and will have no further RECIST assessments.

For screening failures (ie, patients who do not receive study treatment), SAEs will be collected from the time of signature of 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
- CTC grade changes for events of Grade 3 or above
- 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

- 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 investigational product) 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 (see Toxicity Guidelines - Appendix G) 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 and 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 Appendix G.

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca/MedImmune representatives (ie, immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca/MedImmune representative (ie, 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 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.

### 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 in the absence of confirmed PD) and Table 3 (follow-up for patients discontinuing due to confirmed PD). Please also refer to the Laboratory Manual.

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[a] | Red blood cell count |
| Lymphocytes | Total white cell count |
| Mean corpuscular haemoglobin | |

[a] Activated partial thromboplastin time and the international normalised ratio will be performed at Screening and if 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[c] |
| Amylase[c] | Magnesium[c] |
| Aspartate aminotransferase[a] | Potassium |
| Bicarbonate | Sodium |
| Calcium | Total bilirubin[a] |
| Chloride | Total protein |

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

| | |
|---|---|
| Creatinine (creatinine clearance)[c] | Urea or blood urea nitrogen, depending on local practice |
| Gamma-glutamyl transferase[b] | Uric acid[c] |

[a] Tests for aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin must be conducted concurrently and assessed concurrently.
[b] Gamma-glutamyl transferase tested at Screening, Day 1 and as clinically indicated.
[c] Amylase, lipase, creatinine clearance, magnesium and uric acid tested at Screening and every 4 weeks thereafter (ie, every second dosing visit).
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 MEDI4736 should have a further liver chemistry profile (AST, ALT, bilirubin and alkaline phosphatase) performed 30 days (±7days) after permanent discontinuation of MEDI4736.

**Table 7 Urinalysis[a]**

| | |
|---|---|
| Bilirubin | pH |
| Blood | Protein |
| Glucose | Specific gravity |
| Ketones | Colour and appearance |

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.
Urinalysis to be performed at Screening, Day 1, every 4 weeks of MEDI4736 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 investigational product 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 in the absence of confirmed PD] and Table 3 [for follow-up of patients discontinuing due to confirmed PD]).

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:

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

5. 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.

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

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

8. Completely disabled, unable to carry out any self-care and confined totally to bed or chair.

9. Dead

### 6.4.7 Electrocardiogram

Resting 12-lead ECGs will be analysed locally according 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 in the absence of confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD). Note: On Day 1 and Week 16, ECGs should be recorded within an hour prior to the start of the infusion, within 30 minutes post-infusion, and 3 hours (±15 minutes) post-infusion.

Paper tracings will be used for local management, but a digital copy of all ECGs will be held centrally by a central ECG provider, and the data from this review will be stored for analysis at the end of the study. The independent review will not replace the local review by the investigator or cardiologist. Clinical interpretation and management of patients for all ECGs will be done locally.

The same method of assessment should be used throughout.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. All 12-lead ECGs should be recorded while the patient is in the supine position. ECGs should be performed in triplicate with a 2 to 5 minute time lag between each measurement. Further ECGs will be performed when clinically indicated, eg, in the event of a cardiac AE. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. The investigator should record that the ECG has been clinically evaluated, but no interval data should be recorded on the eCRF.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF (see Section 6.4.3).

At screening, mean QTc with Bazett's correction (QTc = QT/√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 in the absence of confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD).

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 BP, pulse, respiratory rate, temperature and oxygen saturation 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 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. Prothrombin time, APTT and INR only performed at Screening unless clinically indicated.
- Hepatitis B and C testing as per local practice
- HIV-1 antibody
- 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 in the absence of confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD).

## 6.5 Pharmacokinetics

### 6.5.1 Collection of samples

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 in the absence of confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD).

Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual. For blood volume see Section 7.1.

### 6.5.2 Determination of drug concentration

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 AstraZeneca/MedImmune, using a validated electrochemiluminescence assay. The lower limit of quantification of MEDI4736 in serum is 50 ng/mL.

### 6.5.3 Antidrug 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 in the absence of confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD).

Samples will be measured for the presence of ADA using a validated electrochemiluminescence assay using a Meso Scale Discovery platform. 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. Samples confirmed positive may also be evaluated for neutralising antibody activity.

## 6.6 Biomarker analysis

Mandatory tumour and blood biomarkers to be evaluated for the purposes of patient selection and for exploratory analyses are described in Section 6.6.1. Exploratory biomarkers may be evaluated as determined by additional data (Section 6.6.2)

Select biomarker assessments that have demonstrated the potential to identify patients who are likely to respond to treatment with MEDI4736 (from other MEDI4736 studies) may be investigated to determine a patient's biomarker status and for possible correlation with efficacy endpoints in an exploratory analysis outside the scope of the CSR.

Exploratory biomarker research 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.

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 in the absence of confirmed PD) and Table 3 (for follow-up of patients discontinuing due to confirmed PD). For blood volume see Section 7.1.

### 6.6.1 Collection of patient selection biomarker data

At Pre-screening, there are two mandatory provisions of tissue:

- A recent (≤3 months) image-guided core needle (at least 18 gauge) tumour biopsy sample taken following the completion of the most recent systemic anti-cancer therapy performed according to institutional practice, except if technically not feasible and after discussion with the study physician.

  If feasible, 4 core samples will be obtained, but a minimum of at least 3 core samples are required. The first and third core samples will be placed in formalin and processed as described in the Laboratory Manual, while the second and fourth

core samples (fourth sample, if available) will be immediately frozen and processed (see the Laboratory Manual).

The sample provided should be a quantity sufficient to allow for analysis (see the Laboratory Manual); however, it is accepted that this may not be feasible in some cases.

If additional tumour biopsies are collected as part of clinical care (eg, for mixed responses or upon PD), they can be submitted for further analysis.

Tumour lesions planned for biopsy must not be used as index lesions for assessment of disease.

- An archived tumour tissue block (formalin-fixed paraffin-embedded) where such samples exist in a quantity sufficient to allow for analysis.

  If an archived tumour block cannot be provided, after discussion with the study physician, 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.

Please review the Laboratory Manual for additional details.

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 PD-L1 immunohistochemistry assay will be used to determine PD-L1 immunohistochemistry status in this study and total tumour membrane staining (percent). The PD-L1 1HC analysis will be performed in the CAP/CLIA laboratory at .

### 6.6.2 Collection of exploratory biomarker data

#### 6.6.2.1 Blood borne biomarkers

Blood (plasma) samples 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 samples will be analysed to evaluate protein, nucleic acid, and cellular biomarkers that relate to MEDI4736 treatment.

Blood (plasma) 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 analyzed 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.

#### 6.6.2.2 Tumour samples

The expression and localization of other immune-related or response-related markers by immunohistochemistry may also include, but may not be limited to, 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, ALK* and the met proto oncogene to evaluate their potential relevance and correlations with response to MEDI4736 treatment.

#### 6.6.2.3 Pharmacogenetics (RNA)

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.

### 6.6.3 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.

## 6.7 Pharmacogenetics

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

# 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 MEDI4736. 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).

**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 | 5 | **5.0** |
| | Coagulation | 3.0 | 1 | **3.0** |
| Pharmacokinetic(s) | | 3.5 | 3 | **10.5** |
| Biomarkers | Soluble PD-L1(to assess target engagement) | 3.5 | 1 | **3.5** |
| | 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 | 5 | **25.0** |
| | miRNA/mRNA (to examine immune cell gene expression profiles in circulation) | 5.0 mL sample at Screening<br>2.5 mL at other timepoints | 5 | **15.0** |
| Pharmacogenetic(s) | | 9.0 | 1 | **9.0** |
| **Total** | | **47 mL** | **40** | **115.0 mL** |

ADA Anti-drug antibody; hCG Human chorionic gonadotropin; 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 and/or pharmacodynamic samples

Samples will be archived for a minimum of 5 years after the Biologic License Application. For sample processing, handling and shipment refer to the investigator's 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.

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 Conference on 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, the study 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, 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 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

At Pre-screening, 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 for patients who achieve disease control at 12 months and restart treatment upon evidence of PD, with or without confirmation, 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. The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression and retreatment as specified in Section 4.3. The 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.

## 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

is responsible for the management of this study and thus throughout this section 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 Web-Based Data Capture system(s) utilised.

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

## 9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).

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

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

**Source data**

Refer to the Clinical Study Agreement for the location of source data.

## 9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

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

**Archiving of study documents**

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

## 9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q2 2014 and to end by Q3 2017.

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

The data cut-off for the final analysis of OS will take place approximately 12 months after the last patient is enrolled in each cohort. At this time point for the final cohort to be analysed, the clinical study database will closed to new data. Patients who are receiving treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit, patients may continue to receive investigational product. All patients

will receive follow-up care in accordance with standard local clinical practice. For patients who do continue to receive treatment beyond the time of the final data cut-off, investigators will continue to report all SAEs to until 90 days after investigational product is discontinued, in accordance with Section 6.4.4 (Reporting of Serious Adverse Events). Additionally as stated in Section 6.4.3 (Recording of adverse events), any SAE or non-serious AE that is ongoing at the time of this data cut-off must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

# 10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by

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 with additional details to support analyses specified in the protocol.

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

### 11.1.1 RECIST 1.1 based endpoints

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

The ICR 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 ICR. Prior radiotherapy reports will also be provided to the ICR 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 ICR will define the overall visit response data (CR, PR, SD, PD or not evaluable) 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 (unless there is evidence of progression in which case the response will be assigned as PD). All RECIST endpoints will be derived from the overall visit response date and the scan dates.

Further details of the ICR will be documented in the ICR 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 treatment or receives another anti-cancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to randomisation. If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of 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, SD and PD.

### 11.1.2 Independent Central Review of irRECIST 1.1-based assessments

To support an exploratory objective of response to therapy by irRC, the ICR of all radiological imaging data will also be carried out using irRECIST as outlined by (Nishino et al 2013).

The criteria that built the foundation for irRC were the WHO criteria which existed before the publication of RECIST 1.1. irRC are, therefore, like WHO criteria, based on bi-dimensional

measurements (Wolchok et al 2009). More recently RECIST 1.1 has become the gold standard for disease status determination in solid tumours. To be more in line with RECIST 1.1 criteria, irRC has been adjusted so that uni-dimensional measurements are used (referred to as irRECIST 1.1). This modification of irRC 2009 criteria (irRECIST 1.1) is suggested based on the results of Nishino et al 2013 who found that irRC using the uni-dimensional measurements provide highly concordant response assessment compared with the bi-dimensional irRC, with less measurement variability. Furthermore, this enables a consistency with RECIST 1.1 which enables a clearer contrast of the results from the two methods than would otherwise be possible.

The definitions of CR, PR, SD and PD according to irRECIST 1.1 will be outlined clearly in the ICR charter.

### 11.1.3 Objective response rate

The primary endpoint is ORR. ORR (per RECIST 1.1 as assessed by the ICR) is defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on a subset of all treated patients. If the ICR finds any patients do not have measurable disease at baseline then the analysis of ORR for the ICR data will exclude these patients, so that the denominator is a subset of all treated patients who have measurable disease at baseline per ICR. However, for Cohort 2, a sensitivity analysis will be performed where the analysis of ORR for the ICR data will include these patients (ie, based upon all treated patients with measurable disease at baseline per the site investigator).

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

ORR will also be obtained using the algorithm described above for the RECIST site investigator tumour data. The denominator for ORR will be all treated patients with measurable disease at baseline per the site investigator.

Additionally, ORR will be obtained using the algorithm described above from the RECIST ICR tumour 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 irRECIST 1.1 data obtained from ICR. Responses of CR/PR also need confirmation under this approach.

### 11.1.4 Duration of response

Duration of response (per RECIST 1.1 as assessed by the ICR) will be defined as the time from the date of first documented response (which is subsequently confirmed) 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 11.1.7).

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR that is subsequently confirmed.

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

Duration of response will not be defined for those patients who do not have confirmed response.

Duration of response will also be obtained using the algorithm described above for the RECIST site investigator tumour data.

For exploratory purposes, DoR will also be obtained using the irRECIST 1.1 data obtained from ICR. Both responses and disease progressions also need confirmation under this approach.

### 11.1.5 Disease control rate

The DCR at 6 months is defined as the percentage of patients who have a BoR of CR or PR in the first 6 months or who have demonstrated SD for a minimum interval of 24 weeks (-7 days, ie, 161 days) following the start of treatment. DCR at 12 months is defined as the percentage of patients who have a BoR of CR or PR in the first 12 months or who have demonstrated SD for a minimum interval of 48 weeks (-7 days, ie, 329 days) following the start of treatment.

Disease control rate will be determined programmatically based on RECIST using ICR data using all data up until the first progression event.

Disease control rate at other timepoints may also be analysed as appropriate.

Disease control rate will also be derived for the RECIST site investigator data.

For exploratory purposes, DCR will also be obtained using the irRECIST 1.1 data obtained from ICR. Disease progressions will need confirmation under this approach.

### 11.1.6 Time to response

Time to response (per RECIST 1.1 as assessed by the ICR) is defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed). The date of first documented response should coincide with that used for the RECIST 1.1 DoR endpoint.

Time to response will not be defined for those patients who do not have confirmed response. Time to response will also be derived for the RECIST site investigator data.

For exploratory purposes, TTR will also be obtained using the irRECIST 1.1 data obtained from ICR. Disease progressions will need confirmation under this approach.

### 11.1.7 Progression free survival

Progression free survival (per RECIST 1.1 as assessed by the ICR) will be defined as the time from the date of first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline.

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

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

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression.

- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

In the absence of clinically significant deterioration the investigational site is advised to continue the patient on MEDI4736 until progression has been confirmed.

For exploratory purposes, PFS will also be obtained using the irRECIST 1.1 data obtained from ICR. Objective disease progressions will require confirmation under this approach.

### 11.1.8 Overall survival

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

Note: Survival calls will be made in the week following the date of data cut-off for the analysis, and if patients are confirmed to be alive or if the death date is after the data cut-off date these patients will be censored at the date of data cut-off. The status of ongoing, withdrawn (from the study) and “lost to follow-up” patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient’s notes, hospital

records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly-available resources where it is possible to do so under applicable local laws.

### 11.1.9 Proportion of patients alive at 6 months and 12 months

The proportion of patients alive at 6 months and 12 months will be defined as the Kaplan-Meier estimate of OS at 6 months and 12 months.

### 11.1.10 Proportion of patients alive and progression free at 6 months and 12 months

The proportion of patients alive and progression free at 6 months (APF6) and alive and progression free at 12 months (APF12) will be respectively defined as the Kaplan-Meier estimate of PFS at 6 months and 12 months.

## 11.2 Calculation or derivation of safety variable(s)

### 11.2.1 Adverse events

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.

Any AE occurring before treatment with MEDI4736 will be included in the data listings but will not be included in the summary tables of AEs.

Adverse events observed up until 90 days following discontinuation of MEDI4736 treatment or until the initiation of the first subsequent therapy following discontinuation of MEDI4736 treatment (whichever occurs first) will be used for reporting of all of the AE summary tables. This will more accurately depict AEs attributable to MEDI4736 only as a number of AEs up to 90 days following discontinuation of MEDI4736 are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of MEDI4736 treatment (ie without taking subsequent therapy into account). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of MEDI4736) will be flagged in the data listings.

### 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 production of outputs for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of investigational product.

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

Corrected Calcium (mmol/L) = Total Calcium (mmol/L) + ([40 – Albumin (G/L)] 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 pharmacokinetic variables

### 11.3.1 PK non-compartmental analysis

The PK sample analyses will be performed at AstraZeneca/MedImmune R&D. The actual sampling times will be used in the PK calculations. MEDI4736 concentration data and summary statistics will be tabulated. Individual and mean blood MEDI4736 concentration-time profiles will be generated. 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 and trough concentration (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

### 11.3.2 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 end points will be evaluated. The results of such an analysis will be reported in a separate report.

### 11.3.3 Immunogenicity analysis

Immunogenicity results will be analysed descriptively by summarizing the number and percentage of patients who develop detectable anti-MEDI4736 antibodies. The immunogenicity titre will be reported for samples confirmed positive for the presence of anti-MEDI4736 antibodies. The effect of immunogenicity on PK, pharmacodynamics, efficacy and safety will be evaluated.

## 11.4 Calculation or derivation of biomarker variable(s)

PD-L1 expression status (positive, negative) is defined as previously described (see Section 3.1).

## 11.5 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).

# 12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

## 12.1 Description of analysis sets

A comprehensive SAP will be prepared with additional details to support analyses specified in the protocol. Table 9 gives a summary of outcome variables and analysis populations. The analysis of Cohort 2 requires some further considerations which are detailed further in Section 12.2.

**Table 9 Summary of outcome variables and analysis populations**

| Outcome variable | Populations |
|---|---|
| **Efficacy Data** | |
| ORR | FAS (ITT) |
| DoR, DCR, TTR, PFS, and OS, proportion of patients alive at 6 and 12 months, APF6, APF12 | FAS (ITT) |
| Demography | FAS (ITT) |
| World Health Organisation performance status | FAS (ITT) |
| PK data | PK |
| **Safety Data** | |
| Exposure | Safety |
| Adverse events | Safety |
| Laboratory measurements | Safety |
| Vital Signs | Safety |

APF6 Alive and Progression Free at 6 months; APF12 Alive and Progression Free at 12 months; DCR Disease control rate; DoR Duration of response; FAS Full analysis set; ITT Intent-to-Treat; ORR Objective response rate; OS Overall survival; PFS Progression free survival; PK Pharmacokinetic; TTR Time to response.

### 12.1.1 Full analysis set (FAS)

Intention-to-treat: The statistical analysis of the efficacy of MEDI4736 will include all treated patients who have a baseline tumour assessment and have measurable disease at baseline according to the investigator site assessment. Patients who were enrolled but did not subsequently go on to receive investigational product are not included in the FAS population. This analysis set will be subsetted for the primary statistical analysis of the efficacy of MEDI4736 for ORR; namely all treated patients who have a baseline tumour assessment and have measurable disease at baseline according to the ICR.

### 12.1.2 Safety analysis set

All patients who received at least 1 dose of investigational product will be included in the safety population. 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.

## 12.2 Methods of statistical analyses

Generally, all analyses and reporting will be separated for each cohort. However, an exploratory analysis will be undertaken where Cohorts 1 and 2 are combined. Cohort 1 will include patients who are *EGFR/ALK* positive. Cohorts 2 and 3 will include patients with *EGFR/ALK* wild type status (ie, do not have *EGFR* TK mutations or *ALK* alterations or where *EGFR* TK mutation/*ALK* fusion status is unknown).

Exploratory testing of biological samples will be conducted after patients have entered this study, and this may include testing for *EGFR* mutation/*ALK* fusion status. If a patient entered the study with unknown *EGFR* TK mutation/*ALK* fusion status and is subsequently found to be *EGFR/ALK* positive, and during their treatment history they have received an EGFR or ALK TKI, they will be re-assigned to the *EGFR/ALK* positive cohort for the final data analysis. Patients with unknown status who are found to be *EGFR/ALK* positive but who have not received an EGFR or ALK TKI prior to entering the study will remain in the *EGFR/ALK* wild type cohort (see Section 3.2 for rationale). It is anticipated that the number of patients re-assigned to the *EGFR/ALK* positive cohort in this way will be very low. However, if there is a sufficient number of re-assignments that would compromise the number of patients available for the efficacy analysis in the *EGFR/ALK* wild type cohorts then further recruitment of patients to those cohorts may be necessary.

It is anticipated that Cohort 2 will be analysed first followed by Cohort 1 and then, finally, Cohort 3. In addition to presentation for each cohort, the safety data may be aggregated and presented overall at the time of the reporting of the second and third cohorts.

Subsequent to the availability of the PD-L1 diagnostic to determine PD-L1 positive patients at the ≥25% cut-point, only those patients with a tumour that is determined to be PD-L1 positive from a central test are permitted into the study. In the case of those patients who were already recruited prior to the availability of this PD-L1 diagnostic, a PD-L1 status can be determined retrospectively based on the patient's pre-treatment tumour sample. The diagnostic itself has been based upon data external to this study (eg, from Study 1108) and the retrospective PD-L1 testing in this study has been completed only after the diagnostic, including the selected 25% threshold, was made available by Results generated to date have not retrospectively influenced this 25% cut-point selection. Similarly, the decision to use the ≥90% cut-point in Cohort 3 was based upon data external to this study (Study 1108). For Cohorts 1 and 2, the analysis of PD-L1 positive patients will include all patients regardless of whether their PD-L1 status was determined prospectively or retrospectively.

For each cohort, the data cut-off for the analysis of ORR will take place approximately 24 weeks after the last patient is enrolled into each cohort.

The data cut-off for the final analysis of OS (secondary endpoint) will take place approximately 12 months after the last patient is enrolled into each cohort.

Descriptive statistics will be used for all variables, as appropriate. 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 and for each cohort.

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

Efficacy data will be summarised and analysed on the FAS (ie, it will follow the Intention to treat principle) and the FAS subset for measurable disease per ICR for the ORR primary analysis.

The primary analysis population of Cohorts 1 and 3 for the primary endpoint, ORR, and for the secondary endpoints is as follows:

- Cohort 1: PD-L1 positive patients (≥25% of tumour cells with membrane staining)
- Cohort 3: PD-L1 positive patients with ≥90% of tumour cells with membrane staining

In Cohort 2, ORR in the PD-L1 positive group (≥25% of tumour cells with membrane staining) is the primary endpoint. Objective response rate in the non-squamous PD-L1 positive (≥25% of tumour cells with membrane staining) group, the ≥90% PD-L1 positive group (≥90% of tumour cells with membrane staining), the ≥90% PD-L1 positive group and the non-squamous ≥90% PD-L1 positive group are key secondary endpoints.

For Cohort 2, the primary efficacy analysis of ORR will be upon the RECIST data based upon the ICR assessments. This will be primarily based upon all treated patients who have a baseline tumour assessment and have measurable disease at baseline according to the ICR. However, a sensitivity analysis will be performed upon all treated patients who have a baseline tumour assessment and have measurable disease at baseline according to the investigator (ie, the FAS). Other major efficacy endpoints using RECIST data based upon the ICR assessments will also have sensitivity analyses performed.

In Cohort 2, all the secondary efficacy endpoints will also be assessed for the non-squamous PD-L1 positive patients, the ≥90% PD-L1 positive patients and the non-squamous ≥90% PD-L1 positive patients. Furthermore, all efficacy will be assessed on PD-L1 negative patients, non-squamous PD-L1 negative patients, PD-L1 unselected patients, the <90% PD-L1 patients (<90% of tumour cells with membrane staining) and the non-squamous <90% PD-L1 patients.

Safety presentations will show the PD-L1 positive patients, non-squamous PD-L1 positive patients, ≥90% PD-L1 positive patients, non-squamous ≥90% PD-L1 positive patients and all patients treated in Cohort 2.

Efficacy will also be investigated for a combined population of Cohorts 2 and 3 for PD-L1 positive patients with ≥90% of tumour cells with membrane staining and also for non-squamous PD-L1 positive patients with ≥90% of tumour cells with membrane staining.

In the subsequent efficacy and safety sections that follow, all analysis described as being 'by cohort' will use the above considerations with regards to the sub-populations to be presented.

A small number of exploratory outputs will investigate efficacy in the PD-L1 negative patients for Cohort 1 (should there be sufficient PD-L1 negative patients to warrant such an analysis), and additionally, for all patients in a combined population of Cohorts 1 and 2.

Safety data will be summarised based on the safety analysis set. No statistical hypothesis will be tested on efficacy and safety endpoints.

### 12.2.1 Objective response rate

The primary endpoint, ORR, will be estimated for each cohort with 95% exact CIs. The primary analysis will be based on the programmatically derived ORR based on ICR assessments, and using all scans regardless of whether they were scheduled or not. An analysis of ORR using the results of the programmatically derived RECIST using the site investigator tumour data from all scans will be conducted as a sensitivity analysis to confirm the results of the primary analysis using data derived from the eCRFs. An additional sensitivity analysis will be performed on programmatically derived ORR using ICR data (RECIST modified for confirmation of progression) to determine if there is any difference when using progression confirmation rules. The primary analysis population for ORR will be a subset of the FAS population (ie, dosed patients with a baseline tumour assessment that indicates measurable disease per the ICR).

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

Summaries of ORR for each cohort will also be presented for the irRECIST 1.1 data obtained from the ICR.

A supportive analysis of patients with unselected PD-L1 status will be conducted consisting of a combined population of PD-L1 positive and PD-L1 negative/unknown patients, including those also enrolled after the protocol amendment to only recruit patients with PD-L1 positive status (ie, all Cohort 2 patients). This will use a weighted approach based on the observed

prevalence of PD-L1 positive, PD-L1 negative and PD-L1 unknown patients from the unselected sample pre-amendment. Further details of this approach will be provided in the SAP.

Furthermore, summaries of ORR (using the programmatically derived ORR based on ICR assessments) may also be presented by cohort for the PD-L1 negative patients in Cohort 1, and additionally, for all patients in a combined population of Cohorts 1 and 2.

### 12.2.2 Duration of response

Kaplan Meier plots of DoR based on the ICR assessment of RECIST will be presented for each cohort. Median DoR will also be summarised. Only patients who have a confirmed response will be included in this summary table. Duration of response will also be analysed based upon the site investigator tumour data.

The DoR will also be summarised using the irRECIST 1.1 data obtained from ICR.

Furthermore, DoR (using the programmatically derived DoR based on ICR assessments) may also be summarised by cohort for the PD-L1 negative patients in Cohort 1 and, additionally, for all patients in a combined population of Cohorts 1 and 2.

### 12.2.3 Disease control rate

The DCR based upon the ICR assessment of RECIST will be summarised (ie, number of patients [%] for each cohort). Disease control rate will also be summarised based upon the site investigator tumour data.

Disease control rate will also be summarised using the irRECIST 1.1 data obtained from ICR.

### 12.2.4 Time to response

The TTR, based upon the ICR assessment of RECIST, will be summarised (ie, number of patients [%] based upon the number of responders for each cohort) by the scheduled assessment timepoint that the response was first observed. Additionally, descriptive summary statistics (ie, minimum, maximum, median, Q1 and Q3) will also be presented. Time to response will also be summarised based upon the site investigator tumour data.

Time to response will also be summarised using the irRECIST 1.1 data obtained from ICR.

### 12.2.5 Progression free survival

Kaplan-Meier plots of PFS will be presented for each cohort. 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 cohort. The proportion of patients APF6 and APF12 will be summarised (using the Kaplan-Meier curve) and presented for each cohort.

Summaries and Kaplan-Meier plots of PFS for each cohort will also be provided using the irRECIST 1.1 data obtained from ICR.

Furthermore, summaries and Kaplan-Meier plots of PFS (using the programmatically derived PFS based on ICR assessments) may also be presented by cohort for the PD-L1 negative patients in Cohort 1, and additionally, for all patients in a combined population of Cohorts 1 and 2.

### 12.2.6 Overall survival

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

The proportion of patients alive at 6 and 12 months will be summarised (using the Kaplan-Meier curve) and presented for each cohort.

Furthermore, OS may also be summarised by cohort for the PD-L1 negative patients in Cohort 1, and additionally, for all patients in a combined population of Cohorts 1 and 2.

### 12.2.7 Safety data

Safety and tolerability data will be presented for each cohort using the safety population.

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 CTCAE grade for each cohort.

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

### 12.2.8 PK data

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

### 12.2.9 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 will be listed for samples confirmed positive for the presence of anti-MEDI4736 antibodies.

### 12.2.10 PK/pharmacodynamic relationships

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

### 12.2.11 Biomarker data

Summaries and analyses for exploratory biomarkers will be reported outside the CSR in a separate report.

### 12.2.12 Interim analysis

An interim analysis of Cohort 2 will be performed after all patients have received one dose of study therapy. This analysis will include preliminary evaluation of efficacy and safety results on PD-L1 positive treated patients.

Additional interim analyses may also be conducted after a minimum follow-up of 8 and 12 weeks respectively from the last treated patient in Cohort 2. The primary efficacy analysis population for these analyses will be the treated PD-L1 positive patients with measurable disease at baseline per the ICR who have had an opportunity of being followed up for at least 24 weeks by the interim analysis DCO. A supportive efficacy analysis will be based on the treated PD-L1 positive patients with measurable disease at baseline per the ICR who have had an opportunity of being followed up for at least 16 weeks by the interim analysis DCO. The interim analysis will be performed on ORR, DoR, DCR, TTR, PFS, OS and key safety endpoints.

The purpose of these interim analyses will be for early evaluation of efficacy and safety data for potential interactions with regulatory agencies on future development of MEDI4736. There are no plans to stop the study early based on these interim results and no formal statistical adjustments are planned. The primary efficacy analysis will take place approximately 24 weeks after the last patient is enrolled into the cohort.

Separate interim analyses of the combined population of Cohorts 2 and 3 for ≥90% PD-L1 positive patients will be performed after approximately 100 patients in this group have had the opportunity to be followed up for at least 8 weeks. At this time, similar analyses will be performed for the non-squamous ≥90% PD-L1 positive patients. These analyses will follow a similar approach to that mentioned above for the Cohort 2 interim analyses performed at the 8 and 12 week minimum follow-up periods.

## 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.

Objective response rate is the primary endpoint. This study will comprise 3 cohorts:

- Cohort 1: *EGFR/ALK* positive, PD-L1 positive patients (defined as ≥25% of tumour cells with membrane staining)
- Cohort 2: *EGFR/ALK* wild type, PD-L1 positive patients (defined as ≥25% of tumour cells with membrane staining)

- Cohort 3: *EGFR/ALK* wild type, PD-L1 positive patients with ≥90% of tumour cells with membrane staining

It is planned to have approximately 94 patients with tumours prospectively determined to be PD-L1 positive (as defined above) in each of the Cohorts 1 and 2. As the diagnostic to determine PD-L1 status was not available when the study first started there will be a number of patients in Cohorts 1 and 2 with tumours determined to be PD-L1 negative, PD-L1 positive or possibly unknown (based retrospectively on the patient's pre-treatment tumour sample).

The study is designed to estimate the response rates for at least 80 evaluable patients in each cohort. This assumes that approximately 15% of patients in each cohort will not be eligible for the primary analysis due to being assessed as having measurable disease by the investigator but not ICR (Douillard et al 2013).

The total number treated in each of the first 2 cohorts is dependent upon the number of patients already treated when the PD-L1 assay cut-off became available and the status of those patients. For example, if 10 patients have been treated in Cohort 1 and 3 of those patients are PD-L1 positive and 7 are PD-L1 negative then a further 91 PD-L1 positive patients will be treated to obtain 94 PD-L1 positive patients in that cohort. In this example the total number of patients in the cohort would be 101 (ie, 94 positive and 7 negative).

In the case of each cohort of 94 patients who have measurable disease per the site investigator and assuming that 80 patients have measurable disease per the ICR, the 2-sided exact 95% CI for the ORR will be (16.0%, 35.9%) provided the observed ORR is 25.0% (based upon 20 patients responding out of 80 patients). Similarly, if the observed ORR is 40.0% (based upon 32 patients responding out of 80 patients) then a 2-sided 95% CI for the ORR will be (29.2%, 51.6%).

## 12.4 Data monitoring committee

Not applicable.

# 13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

## 13.1 Medical emergencies, AstraZeneca/MedImmune and 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**

| Name | Role in the study | Address & telephone number |
|---|---|---|
| | Study Delivery Team Leader | |
| | Study Physician | |
| Patient Safety | MedImmune Patient Safety | |

## 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 Case Report Form module.

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

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

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

## 13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca representative (ie,

### 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, investigators or other site personnel must inform appropriate AstraZeneca representatives (ie, immediately, or **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca/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.

### 13.3.2 Paternal exposure

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.

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. 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.

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**Clinical Study Protocol Appendix B**

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| Drug Substance | MEDI4736 |
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# 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.

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**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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# Appendix D
# Pharmacogenetics Research

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| CSR | Clinical Study Report |
| DNA | Deoxyribonucleic acid |
| LIMS | Laboratory information management system |
| PGx | Pharmacogenetics |

# 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 MEDI-4736, 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, subjects must fulfill 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 subjects from this genetic research

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

Withdrawal of consent for genetic research: Subjects 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 (AE), as these patients would be important to include in any genetic analysis. Only one 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 five times to mix thoroughly. Tubes will be identified with the protocol study number, center number, enrollment 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, 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, 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 subject'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 genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca 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 subject 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 analyzed.

# 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 ICH/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 subject 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 subject 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 subject and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

## 4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, 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 subject. 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 subject. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a subject's identity and also have access to his or her genetic data. Regulatory authorities may also require access to the relevant files, though the subject'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 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 subjects 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.

**Revised Clinical Study Protocol Appendix E**

| | |
|---|---|
| Drug Substance | MEDI4736 |
| Study Code | D4191C00003 |
| Edition Number | 1 |
| Date | |

# 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 (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

# 2. DEFINITIONS

**Potential Hy's Law (PHL)**

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 serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

**Hy's Law (HL)**

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 can be found to explain the combination of increases, eg, elevated serum 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 AZ standard processes

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

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

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

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

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

# 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[#] compared with the last visit where PHL criteria were met

  – If there is no significant change no action is required

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

  [#] 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 30-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[#] 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

[#] 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.

# 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

AstraZeneca

**Clinical Study Protocol Appendix F**

| | |
|---|---|
| Drug Substance | MEDI4736 |
| Study Code | D4191C00003 |
| Appendix Edition Number | 2 |
| Appendix Date | |

# Appendix F
# Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

## TABLE OF CONTENTS PAGE

# 1. INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D4191C00003 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

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Tumour lesions selected for screening biopsy must not be used as index lesions.

**Measurable:**

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

**Non-measurable:**

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline[1]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Tumour lesions selected for screening biopsy.
- Previously irradiated lesions[2]
- Skin lesions assessed by clinical examination

[1] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).
[2] Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

- Brain metastasis

**Special cases:**

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

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

**Target lesions:**

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

**Non-target lesions:**

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

# 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 |
| | | FDG-PET |

CT Computed tomography; FDG-PET 18-Fluoro-deoxyglucose positron emission 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 D4191C00003 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 D4191C00003 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 D4191C00003 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 D4191C00003 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 D4191C00003 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 D4191C00003 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 D4191C00003 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

## 3.7 Cytology and histology

In the D4191C00003 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 D4191C00003 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 FDG-PET scan

In the D4191C00003 study, 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive 18-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

[3] A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

# 4. TUMOUR RESPONSE EVALUATION

## 4.1 Schedule of evaluation

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 imaging may be performed based on the signs and symptoms of the patient e.g new lesions at follow-up.

The baseline assessment should be performed no more than 28 days before the start of MEDI4736 treatment and ideally as close as possible to the start of investigational product. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks for the first 48 weeks (relative to the date of the first MEDI4736 infusion; see Table 1 of the Clinical Study Protocol), then every 12 weeks after discontinuation of MEDI4736 in patients who have disease control after 12 months of treatment (Table 2 of the Clinical Study Protocol) until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment/or subsequent therapy). If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

For patients who discontinue MEDI4736 due to toxicity in the absence of confirmed objective progression objective tumour assessments should be continued every 8 weeks for 48 weeks (relative to the date of the first MEDI4736 infusion) then every 12 weeks 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.

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

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.

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.

## 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 should be identified as TL at baseline.

Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in 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 |

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

# 5. CONFIRMATION OF RESPONSE AND PROGRESSION

In the D4191C00003 study, imaging for confirmation of response (complete response or partial response) should be performed at next scheduled visit (and no less than 4 weeks) following the date the criteria for response were first met.

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

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

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits (with an absolute increase of 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.

**Clinical Study Protocol Appendix G**

| | |
|---|---|
| Drug Substance | Durvalumab (MEDI4736) |
| Study Code | D4191C00003 |
| Edition Number | 1.0 |

# Appendix G
# Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion related, and Non Immune-mediated Reactions,

## Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)

1

<table>
<tr><th colspan="3">Immune-Mediated Reactions</th></tr>
<tr><th></th><th>Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td>Immune-related Adverse Events (Overall Management For toxicities not noted below)</td><td>Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.<br>In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions:<br>• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen<br>• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.<br><br>Grade 1 — No dose modification<br><br>Grade 2 — Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1<br>• If toxicity worsens then treat as Grade 3 or Grade 4<br>• If toxicity improves to baseline then treat at next scheduled treatment date<br>Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper<br>Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician’s clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.</td><td>It is recommended that management of irAEs follow the guidelines presented in this table<br>- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.)<br>- In the absence of a clear alternative etiology, all events should be considered potentially immune related.<br>- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events<br>- For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent<br>- If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper)<br>- More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids.<br>- Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient</td></tr>
</table>

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | | | |
|---|---|---|---|
| | Grade 3 | Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below | |
| | Grade 4 | Permanently discontinue study drug/study regimen | |
| | Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen | | |

| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| Pneumonitis/ILD | Grade of Pneumonitis (CTCAE version 4.03) | Any Grade | - Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below<br>- Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan. |
| | Grade 1<br>(Asymptomatic, clinical or diagnostic observations only, intervention not indicated) | No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies | For Grade 1 (Radiographic Changes Only)<br>- Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated<br>- Consider pulmonary and infectious disease consult |
| | Grade 2<br>(Symptomatic, medical intervention indicated, limiting instrumental ADL) | Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1<br>• If toxicity worsens then treat as Grade 3 or Grade 4<br>• If toxicity improves to baseline | For Grade 2 (Mild to Moderate New Symptoms)<br>- Monitor symptoms daily and consider hospitalization<br>- Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day or IV equivalent)<br>- Reimaging as clinically indicated |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment.<br>Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper | - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started<br>- If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab<br>- Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii1]<br>- Consider pulmonary and infectious disease consult<br>- Consider as necessary discussing with study physician |
| | Grade 3 or 4<br>(Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated;<br><br>Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation]) | Permanently discontinue study drug/study regimen | For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening<br>- Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent<br>- Obtain pulmonary and infectious disease consult<br>- Hospitalize the patient<br>- Supportive Care (oxygen, etc.)<br>- If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii] |

[1] ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| Diarrhea/ Enterocolitis | Grade of Diarrhea (CTCAE version 4.03) | Any Grade | - Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus)<br>- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.)<br>- Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event<br>- Use analgesics carefully; they can mask symptoms of perforation and peritonitis |
| | Grade 1 diarrhea (stool frequency of <4 over baseline per day) | No dose modification | For Grade 1 diarrhea :<br>- Close monitoring for worsening symptoms<br>- Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment. |
| | Grade 2 diarrhea (stool frequency of 4-6 over baseline per day) | Hold study drug/study regimen until resolution to ≤ Grade 1<br>• If toxicity worsens then treat as Grade 3 or Grade 4<br>• If toxicity improves to baseline then treat at next scheduled treatment date<br>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid | For Grade 2 diarrhea:<br>- Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide<br>- Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent<br>- If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started.<br>- If still no improvement within 3-5 days despite 2-4mg/kg IV |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | taper | methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[2]). . **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab<br>- Consult study physician if no resolution to ≤ Grade 1 in 3-4 days<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |
| | Grade 3 or 4 diarrhea<br><br>(Grade 3: stool frequency of ≥7 over baseline per day;<br><br>Grade 4: life threatening consequences) | Permanently discontinue study drug/study regimen | For Grade 3 or 4 diarrhea:<br>- Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent<br>- Monitor stool frequency and volume and maintain hydration<br>- Urgent GI consult and imaging and/or colonoscopy as appropriate<br>- If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks).<br>- Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |

[2] ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| Hepatitis (Elevated LFTs)<br>**Infliximab should not be used for management of Immune Related Hepatitis** | Grade of Liver Function Test Elevation (CTCAE version 4.03)<br>Any Grade<br>Grade 1<br>(AST or ALT > ULN to 3 times ULN and/or TB > ULN to 1.5 times ULN) | No dose modification<br>If it worsens, treat as Grade 2 event | - Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin<br>- Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)<br>For Grade 1 AST or ALT and/or TB elevation<br>- Continue LFT monitoring per protocol |
| | Grade 2<br>(AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times ULN) | Hold Study drug/study regimen dose until grade 2 resolution to ≤ Grade 1<br>• If toxicity worsens then treat as Grade 3 or Grade 4<br>• If improves to baseline then treat at next scheduled treatment date<br>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper | For Grade 2 AST or ALT and or TB elevation :<br>- Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved.<br>- If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician.<br>- If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day or IV equivalent.<br>- If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started.<br>- If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[3] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**.<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to |

[3] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" , by Michael Postow MD

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | | current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |
| | Grade 3<br>(AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN | For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN<br>-Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline<br>-Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline within 14 days<br>Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days<br>For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen<br>Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT > | For Grade 3 or 4 AST or ALT and/or TB elevation:<br>- Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent<br>- If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent , promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**<br>- Hepatology consult, abdominal workup, and imaging as appropriate.<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| | | 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[iv] | |
| | Grade 4<br>(AST or ALT > 20 times ULN and/or TB > 10 times ULN) | Permanently discontinue study drug/study regimen | |
| Nephritis or Renal Dysfunction (Elevated Serum Creatinine) | Grade of Elevated Serum Creatinine (CTCAE version 4.03)<br><br>Any Grade | | - Consult with Nephrologist<br>- Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.)<br>- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)<br>- Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| | Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN] | No dose modification | For Grade 1 elevated creatinine:<br>- Monitor serum creatinine weekly and any accompanying symptom<br>• If creatinine returns to baseline, resume its regular monitoring per study protocol.<br>• If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4<br>- Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. |
| | Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN] | Hold study drug/study regimen until resolution to ≤ Grade 1<br>• If toxicity worsens then treat as Grade 3 or Grade 4<br>• If toxicity improves to baseline then treat at next scheduled treatment date<br>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 for 5-7 days have passed after completion of steroid taper | For Grade 2 elevated creatinine:<br>- Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.<br>- Carefully monitor serum creatinine every 2-3 days and as clinically warranted<br>- Consult Nephrologist and consider renal biopsy if clinically indicated<br>- If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent<br>- If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started.<br>- Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).<br>- When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol. |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| | Grade 3 or 4<br>(Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN<br><br>Grade 4: Serum Creatinine > 6.0 X ULN) | Permanently discontinue study drug/study regimen | - Carefully monitor serum creatinine on daily basis<br>- Consult Nephrologist and consider renal biopsy if clinically indicated<br>- Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent<br>- If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started.<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation] |
| Rash (excluding Bullous skin formations) | Grade of Skin Rash<br>(Please refer to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash) | Any Grade | Monitor for signs and symptoms of dermatitis (rash and pruritus)<br>**IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED**** |
| | Grade 1 | No dose modification | For Grade 1:<br>- Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) |
| | Grade 2 | For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline<br>• If toxicity worsens then treat | For Grade 2 :<br>- Obtain dermatology consult<br>- Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)<br>- Consider moderate-strength topical steroid<br>- If no improvement of rash/skin lesions occurs within 3-5 days or is |

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| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | as Grade 3<br>• If toxicity improves then resume administration at next scheduled dose<br>• Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper | worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent<br>- Consider skin biopsy if persistent for >1-2 weeks or recurs |
| | Grade 3 | Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline<br>If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen | For Grade 3 or 4:<br>- Consult dermatology<br>- Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent<br>- Consider hospitalization<br>- Monitor extent of rash [Rule of Nines]<br>- Consider skin biopsy (preferably more than 1) as clinically feasible.<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<br>- Discuss with Study Physician |
| | Grade 4 | Permanently discontinue study drug/study regimen | |

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| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.) | Any Grade<br>(Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity) | | - Consult Endocrinologist<br>- Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness.<br>- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.)<br>- Monitor and evaluate thyroid function tests: TSH, free $T_3$ and free $T_4$ and other relevant endocrine labs depending on suspected endocrinopathy.<br>- If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing |
| | Grade 1<br>(Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1) | No dose modification | For Grade 1: (including those with asymptomatic TSH elevation)<br>- Monitor patient with appropriate endocrine function tests<br>- If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult. |

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| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| | Grade 2<br>(Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 2) | For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable<br>• If toxicity worsens then treat as Grade 3 or Grade 4<br>• If toxicity improves to baseline then treat at next scheduled treatment date<br>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper<br>Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled ,2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent. | For Grade 2: (including those with symptomatic endocrinopathy)<br>- Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids<br>- Initiate hormone replacement as needed for management<br>- Evaluate endocrine function, and as clinically indicated, consider pituitary scan<br>- For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). -<br>- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<br>- For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated. |

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| | **Grade of the Event (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
|---|---|---|---|
| | Grade 3 or 4<br>(Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4) | For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled<br>Resume study drug/study regimen administration if controlled at the next scheduled dose<br>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper | For Grade 3 or 4:<br>- Consult endocrinologist<br>- Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids<br>- Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent<br>- Administer hormone replacement therapy as necessary.<br>- For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity<br>- Once improving, gradually taper immunosuppressive steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<br>- Discuss with study physician |
| Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre) | Grade of Neurotoxicity<br>Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for defining the CTC grade/severity | | |
| | Any Grade | | - Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.)<br>- Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness)<br>- Consider appropriate diagnostic testing (e.g. electromyogram and nerve |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | | conduction investigations)<br>- Symptomatic treatment with neurological consult as appropriate |
| | Grade 1 | No dose modifications | See "Any Grade" recommendations above. |
| | Grade 2 | • For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1<br>• For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1.<br>o If toxicity worsens then treat as Grade 3 or Grade 4<br>o If toxicity improves to baseline then treat at next scheduled treatment date<br>• Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper | - Discuss with the study physician<br>- Obtain Neurology Consult<br>- Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.)<br>- Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent<br>- If no improvement within 3-5 days despite 1-2mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG) |
| | Grade 3 | • Hold Study drug/study regimen dose until resolution to ≤ Grade 1 | For Grade 3 or 4:<br>- Discuss with study physician |

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| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | • Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days. | - Obtain Neurology Consult<br>- Consider hospitalization<br>- Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent<br>- If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG)<br>- Once stable, gradually taper steroids over ≥4 weeks |
| | Grade 4 | • Permanently discontinue study drug/study regimen | |
| Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis | | Any Grade | - The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability<br>- Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult<br>- Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation<br>Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | | not responsive to IVIG |
| | Grade 1 | No dose modification | - Discuss with the study physician<br>- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above<br>- Obtain a neurology consult unless the symptoms are very minor and stable |
| | Grade 2 | Hold study drug/study regimen dose until resolution to ≤ Grade 1<br>Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability | Grade 2<br>- Discuss with the study physician<br>- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above<br>- Obtain a Neurology Consult<br>- Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.)<br>*MYASTHENIA GRAVIS*<br>o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.<br>o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.<br>o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.<br>*GUILLAIN-BARRE:*<br>o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. |

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| | Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|---|
| | | | Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG. |
| | Grade 3 | Hold study drug/study regimen dose until resolution to ≤ Grade 1<br>Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability | For severe or life threatening (Grade 3 or 4) events:<br>- Discuss with study physician<br>- Recommend hospitalization<br>- Monitor symptoms and obtain neurological consult<br>*MYASTHENIA GRAVIS*<br>o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist.<br>o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG.<br>o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.<br>*GUILLAIN-BARRE*:<br>Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG |
| | Grade 4 | Permanently discontinue study drug/study regimen | |

**Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)**



| **Infusion-Related Reactions** | | |
|---|---|---|
| Severity Grade | **Dose Modifications** | **Toxicity Management** |
| Any Grade | | - Management per institutional standard at the discretion of investigator<br>- Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.) |
| Grade 1 | The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event | For Grade 1 or Grade 2:<br>- Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator<br>- Consider premedication per institutional standard prior to subsequent doses |
| Grade 2 | The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event<br>Subsequent infusions may be given at 50% of the initial infusion rate | |
| Grade 3/4 | Permanently discontinue study drug/study regimen | For Grade 3 or 4:<br>Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid) |

## Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)



| **Non-immune Mediated Reactions**<br><br>**(Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician"** | | |
|---|---|---|
| **CTC Grade/Severity** | **Dose Modification** | **Toxicity Management** |
| **Any Grade** | Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant. | Treat accordingly as per institutional standard |
| **1** | No dose adjustment | Treat accordingly as per institutional standard |
| **2** | Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline | Treat accordingly as per institutional standard |
| **3** | Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline<br>For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. Otherwise, discontinue study drug/study regimen | Treat accordingly as per institutional standard |
| **4** | Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor) | Treat accordingly as per institutional standard |

Abbreviations:

AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

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[i] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[ii] NCI CTCAE version 4.03
[iii] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[iv] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation