Clinical Study Protocol

Drug Substance	AZD9291/MEDI4736
Study Code	D5165C00001
Version	2.0
Date	02 March 2017

A Phase III, Multi-Centre, Open Label, Randomized Study to Assess the Efficacy and Safety of AZD9291 in Combination with MEDI4736 versus AZD9291 Monotherapy in Patients with Locally Advanced or Metastatic Epidermal Growth Factor Receptor T790M mutation-positive Non-Small Cell Lung Cancer who have received Prior Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy (CAURAL)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 2.0, 02 March 2017

Various Sections – the entire protocol text has been updated to reflect that this study has terminated recruitment early. Early termination of enrolment into the study was decided in the light of a higher than anticipated incidence of ILD-like events in patients receiving the combination of AZD9291 with MEDI4736 in a separate multi-arm Phase 1b open label study D5160C00006 (TATTON) . TATTON was designed to assess the safety, tolerability, PK and preliminary anti-tumour activity of AZD9291 in combination with ascending doses of novel therapeutics, including MEDI4736, in patients with EGFRm+ advanced NSCLC who have progressed following therapy with an EGFR TKI. Following determination of a recommended dose and schedule, a cohort of patients with EGFRm+ advanced NSCLC receiving AZD9291 in combination with MEDI4736 in the first line setting was also enrolled. Given that only 29 patients were randomised into the CAURAL study when recruitment was terminated the sample size in this study is too small to make any formal statistical comparisons of efficacy or safety between arms. The study is being continued to further characterize the safety and tolerability profile of MEDI4736 in combination with AZD9291 and to allow patients who are still showing clinical benefit according to the investigator to continue to receive AZD9291 monotherapy, MEDI4736 in combination with AZD9291 or MEDI4736 monotherapy. The primary objective of the study has been amended and is to assess the safety and tolerability of the combination of AZD9291 and MEDI4736. Given that AZD9291 monotherapy is approved for use in patients with locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) whose disease has progressed on or after EGFR TKI therapy, i.e. the same patient group that is enrolled in CAURAL, ongoing collection of safety information for patients receiving AZD9291monotherapy will be restricted to serious adverse events, outcomes of pregnancy, overdose and drug dispensing/accountability after approval of protocol version 2.0. Monitoring of the patient will be carried out in accordance with the investigator's standard clinical practice or national product label.

Changes to the protocol are summarised below:

Section 1.1 (Disease Background & Section 1.2 (Description of clinical data) - Updated in various sub-sections to include information regarding regulatory approval of AZD9291 and other compounds, patient recruitment and adverse events.

Section 1.3.1 (AZD9291): Safety information has been updated on incidence rate of adverse drug reactions on a set of 411 patients treated at 80mg AZD9291

Section 1.3.3 (Rationale) - Updated to include the most current safety data for the AZD9291+MEDI4736 combination therapy. This is to include the new signal of increased

frequency of ILD with the combination, which lead to changes in the study objectives

Section 1.5 (Benefit and Risk assessment) - The risk benefit assessment has been updated to clarify the approach allowing patients to continue on the combination of MEDI4736 and AZD9291

Section 1.6 (Study Design + Figures) - Updated to include the most current data affecting the risk/benefit analysis for AZD9291+MEDI4736. This is to include the new signal of increased frequency of ILD with this combination, which lead to changes in the study objectives & design

Synopsis & Section 1.6, Figure 1, Section 2 – Text has been updated to indicate the final numbers of patients screened and randomised at the time of termination of patient recruitment

Figure 1 – Updated to include the addition of Group A and Group B to the study design. Group A includes patients continuing to receive AZD9291 monotherapy who were either (i) randomised to receive AZD9291 monotherapy or were (ii) randomised to receive AZD9291 in combination with MEDI4736 but who have discontinued MEDI4736 and been followed up for 90 days post discontinuation of Medi4736. Group B includes patients randomised to receive MEDI4736 and AZD9291 and who are continuing to receive MEDI4736 either in combination with AZD9291 or as monotherapy. Synopsis objectives and Section 2.1 updated with new primary endpoint i.e.to assess the safety and tolerability profile of AZD9291in combination with MEDI4736 in order to reflect the changed nature of the study

Synopsis & Section 2.1 – Updated to remove all secondary objectives and include the following previously assigned secondary objectives as exploratory objectives.

- To assess the safety and tolerability of AZD9291 monotherapy
- To obtain a preliminary assessment of the efficacy of AZD9291 in combination with MEDI4736 and AZD9291 monotherapy
- To assess the PK of AZD9291 in combination with MEDI4736.
- To characterise the PK, immunogenicity and pharmacodynamics of MEDI4736 after single dosing and at steady state after multiple dosing when given intravenously to patients with EGFRm NSCLC in combination with AZD9291.

Synopsis and Section 2 (Study Objectives) -

Removal of all objectives (secondary and exploratory) related to patient reported outcomes and healthcare resource. Also, removal of some exploratory objectives including: post-progression outcomes, PK/PD modelling, exploration of immune-related response criteria as an assessment methodology for clinical benefit and exploration of impact of prognostic factors on OS outcome.

Synopsis & Sections, 8.2, 9.2 - Study duration has been updated to clarify that the study will be complete after the last patient discontinues MEDI43736 and completes the required safety follow up. As the study's primary objective has been amended in light of early termination of enrolment it is considered that this duration of follow up will provide sufficient information to characterize the safety and tolerability profile of the combination of AZD9291 with MEDI4736.

Section 3.5 (Treatment Group) - Updated to describe the categorization of patients into either Group A or Group B following approval of version 2.0 of the clinical study protocol. These patients groups are being implemented to guide study conduct for patients receiving treatment with AZD9291 monotherapy or treatment with MEDI4736 as a monotherapy or in combination with AZD9291

Section 3.6 – Restrictions removed regarding co-administration of CYP3A4 inhibitors with AZD9291 on the basis of information from clinical pharmacology study D5160C00012 A phase I, open-label, non-randomised study to assess the effect of itraconazole (a CYP3A4 Inhibitor) on the pharmacokinetics of a single oral dose of AZD9291 in patients with EGFRm positive NSCLC whose disease has progressed on an EGFR TKI. Based on the pre-specified criteria no effect on the exposure of AZD9291 after co-administration with itraconazole was observed.

Statin use guidance has been updated to reflect results from clinical pharmacology studies (i) study D5160C00014, a phase I, open-label, non-randomised, multicentre study to assess the effect of AZD9291 on the pharmacokinetics of simvastatin (a sensitive CYP3A4 substrate) in patients with EGFRm positive NSCLC whose disease has progressed on an EGFR TKI and (ii) D5160C00019, a phase I, open-label, non-randomised, multicentre study to assess the effect of AZD9291 on the pharmacokinetics of rosuvastatin (a sensitive BCRP Substrate) in patients with EGFRm positive NSCLC whose disease has progressed on an EGFR TKI.

Updated the timeframe contraception methods are recommended to be used after IP discontinuation in female patients to be in line with AstraZeneca's current guidance for both AZD9291 and MEDI4736. Also updated male patients recommended timeframe procreation is to be avoided and contraception methods are to be used after IP discontinuation to match the more conservative recommendations for AZD9291.

3.7 (Discontinuation from IP) - Updated as required per AZD9291 Project Specific Safety Requirements v13

3.7.1 – Discontinuation procedures updated for patient receiving AZD9291 monotherapy or in combination with MEDI4736

Section 4 and Section 5 Tables and applicable text updated to reflect the following changes:

- ECG assessments to be done locally, triplicate no longer required, results will no

longer be stored or assessed centrally

- Completion of Patient Reported Outcomes (EORTC QLQ LC13, EORTC QLQ C30, PRO CTCAE, CTSQ 16) will no longer be required after CSP Version 2.0 is approved.
- Healthcare resource use information will no longer be collected after CSP Version 2.0 is approved
- Table 3 – Updated table to display the follow up schedule required for Group B (AZD9291 & MEDI4736 Combination therapy patients). Also updated to indicate RECIST assessments are not required after the completion of the 90 day follow up period.
- Table 4 – Has been removed as the assessments displayed in this table are now detailed in Table 3 for Group B and Table 1 for Group A

Section 3.9 (Discontinuation from study)- Updated to remove language regarding study stoppage through an interim safety analysis conducted through an IDMC as this is no longer applicable

Section 4 (Tables 1 and 2) updated to reflect current patient schedule

Section 4.2 (Treatment Period) - Text was updated to include patient Groups A & B and to indicate that MEDI4736 or AZD9291 in the combination arm can be terminated at any time due to Investigator judgement or patient decision. Also updated to indicate that patients that stop MEDI4736 during the study can then begin to follow the Group A AZD9291 Monotherapy assessment schedule after the 3 month follow up assessment is completed if still receiving AZD9291. Lastly, the text was updated to reflect that patients randomised to receive combination treatment who discontinue AZD9291 will not be permitted to discontinue MEDI4736 monotherapy and re-start AZD9291 monotherapy.

Section 4.3 (Follow-up period) - Updated to clarify the follow up schedule for Group A- AZD9291 Monotherapy and Group B – AZD9291 & MEDI4736 Combination.

Section 4.4 (Patient Management) - Section added to provide more detail regarding the management after the last patient discontinues MEDI4736

Section 5.1.1, 5.1.2 (Efficacy Assessments) - Text was updated to clarify that imaging scans will not be assessed centrally for this study. Removal of the requirement for blinded independent central review (BICR) was also clarified.

Section 5.2.1 - Separated into sections 5.2.1 and 5.2.2 to clarify Group A and Group B Safety assessments respectively Section 5.3.2 (Patient Reported Outcomes) – Post-progression outcomes are being removed from the study due to the small sample size. Section 6.3.1 (AE collection) - Text has been updated to reflect that no additional safety information will be

collected for the trial after the completion of the required follow up period and to clarify the process regarding collecting SAE, overdose and pregnancy information after the last patient discontinues of MEDI4736.

Section 6.7 (Management of IP related toxicities): This section was modified to reflect the latest Investigator's Brochure (IB) update. A guidance of how to proceed in case of QTcF prolongation to >500 msec on at least 2 separate ECGs was updated. Text has been added to clarify that patients experiencing corneal ulceration, Interstitial Lung Disease (ILD) and QTc interval prolongation with signs/symptoms of serious arrhythmia are not permitted to restart study treatment.

Synopsis & Section 6.8.1 (Data Monitoring) - Text has been updated to reflect that the pre-defined number of enrolled patients required for IDMC review was never achieved and that in light of the early termination of recruitment, limited number of patients dosed in the study and the change in study scope, the IDMC, coordinating investigators and AstraZeneca have agreed that there is no further scope for IDMC to monitor the study.

Section 7.2.1 – (AZD9291) Fasting requirements were removed on the basis of information from the AZD9291 clinical pharmacology study D5160C00009, an open-label, randomised, phase I study to determine the effect of food on the pharmacokinetics of single oral doses of AZD9291 in patients with EGFRm positive NSCLC whose disease has progressed on an EGFR TKI. Administration of AZD9291 80 mg as a tablet following a high fat meal did not affect AZD9291 exposure

Section 7.2.1 (AZD9291) and 7.5 (Compliance): These sections were updated to provide more clarity regarding the drug dispensing and drug accountability process for Group A – AZD9291 Monotherapy patients post CSP Version 2.0approval

Section 7.8 (Post study access to study treatment): Updated to reflect the current strategy for patient management following study completion outlined in section 4.4

Synopsis & Section 8 – (Statistics) The statistical methods were updated to reflect the change in study objectives and reduction in data collection in CSP Version 2.0. The primary objective is to assess the safety and tolerability of the combination of AZD9291 and MEDI4736. Efficacy related objectives are considered exploratory, while all secondary objectives have been removed. Some previously assigned secondary objectives have been reassigned as exploratory objectives and some exploratory objectives have been removed as described above in synopsis objectives. Post the approval of protocol version 2.0, patient's receiving AZD9291 monotherapy will be seen as per their normal routine clinical care, with no clinical data collected other than serious adverse events, outcomes of pregnancy and drug dispensing/accountability. There will be two main summaries of the data presented overall. Safety and tolerability related summaries will comprise of patients who received at least one dose of randomised treatment, where efficacy summaries will use all patients randomised on

the study, regardless of the treatment actually received.

A primary summary will be performed with a data cut-off date representative of when the last country with active patients receives ethics and regulatory approval for protocol version 2.0. If all patients receiving MEDI4736 will discontinue the treatment before the time of protocol version 2.0 is approved in all countries with active patients, no further summary will be performed. At the primary summary, patients will be summarised according to the randomised treatment. All statistical analyses for PFS have been replaced with descriptive summaries of the number of events and percentage (where appropriate) at month 6 and month 12. Kaplan Meier plots will be produced along the summaries. Similarly other efficacy summaries (ORR, DoR, DCR, OS) and safety summaries will be limited to reporting the number of events and percentages. Patients alive and event free will be given at set intervals during follow up. No statistical analyses are performed for time to event analysis unless there are at least 20 events for both treatment arms combined and at least 5 events in each treatment arm.

If any patient continues to receive MEDI4736 after the DCO for the primary study summary, then a final addendum summary will be performed when the last patient discontinues MEDI4736 and completes their required safety follow up. Only data collected between the primary summary data cut-off and the time when last patient receiving MEDI4736 reaches the end of safety follow up, will be summarised. Patients will be summarised by Group A (patients receiving AZD9291 monotherapy either due to randomisation or due to discontinuing MEDI4736) and group B (patients receiving MEDI4736 either as combination or as monotherapy). Available safety data will be summarised and the number of events and percentage will be shown for: all Group A patients, Group A patients who were randomised to AZD9291 monotherapy and Group A patients who were initially randomised to AZD9291 + MEDI4736 treatment, and all group B patients. Patients in Group A will have limited data available for summary as the data collection will be reduced for this group after the primary summary data cut-off. In addition, exploratory summaries will be produced for patients in group B since there will be efficacy data collected for this patients post the approval of protocol version 2.0. Note : If there are less than 3 patients in any Group the safety and efficacy data will be given as a listing only.

In all instances of summaries, due to the small study population caused by early study termination it is not appropriate to perform statistical testing between groups. As a result there will be no hypothesis testing performed. Instead all outcomes will be reported descriptively. Pharmacokinetic concentration data and the ratio of metabolite to AZD9291 will be listed and summarised. The reduction in follow up time has resulted in the removal of further time to event analyses such as time to subsequent treatment.

Section 8.1 (Statistical Considerations) – Updated to clarify the timing of the study analyses.

Section 8.2 – (Sample size) Updated to reflect the early termination of recruitment

Section 8.4.1 – (Calculation or derivation of efficacy variables) The range of data being collected on study post approval of CSP Version 2.0 has been reduced. As such the following

planned analyses have been removed: patient reported outcomes.

Section 8.5 – (Methods for statistical analyses) Updated to indicate that the Baseline and the data collected for the preliminary efficacy data will be summarised using the FAS.

Section 9.2 - (study timetable and end of study): The expected study end date was updated.

Section 11 – References updated

Appendices – The naming and numbering of all Appendices has been updated as applicable

Signatory pages appendix (formally Appendix A) has been removed from the document as the signature process is now completed electronically

Patient Reported Outcomes appendix (Formally Appendix G) has been removed as this assessment is no longer part of the study

Appendix E, Guidance Regarding Potential Interactions with Concomitant Medications – Document has been updated to the most current version available.

Appendix G, MEDI4736 Toxicity Management Guidelines – Safety language has been updated and the guidelines have been added as an appendix to the protocol per new AstraZeneca MEDI4736 program guidance determined in discussion with the FDA.

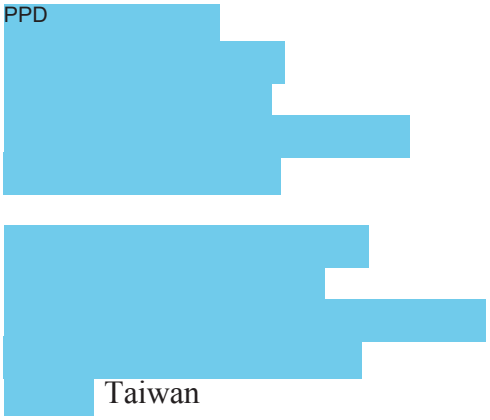
Version 1.0, 13 May 2015
Initial Protocol

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

PROTOCOL SYNOPSIS

A Phase III, Multi-Centre, Open Label, Randomized Study to Assess the Efficacy and Safety of AZD9291 in Combination with MEDI4736 versus AZD9291 Monotherapy in patients with Locally Advanced or Metastatic Epidermal Growth Factor Receptor T790M mutation-positive Non-Small Cell Lung Cancer who have received Prior Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy (CAURAL)

International Co-ordinating Investigators



Study site(s) and number of subjects planned

It was originally planned that approximately 350 patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC; Stage IIIB-IV) will be evaluated from approximately 100 centres in North America, Asia and Europe. As recruitment in this study was terminated early, a total of 29 patients were randomized in Canada, South Korea and Taiwan.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2015	III
Estimated date of last subject completed	Q4 2017	

Study design

This trial was initially designed as a phase III, multi-centre, open label, randomized study to assess the efficacy and safety of AZD9291 (80 mg, orally, once daily) in combination with

MEDI4736 [10 mg/kg (IV) infusion every 2 weeks (q2w)] versus AZD9291 monotherapy (80 mg, orally, once daily) in patients with a confirmed diagnosis of Epidermal Growth Factor Receptor (EGFR) T790M mutation positive (hereafter referred to as EGFR T790M+) NSCLC (Stage IIIB-IV), who have progressed following prior therapy with an approved Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) agent.

Three hundred fifty patients were planned to be enrolled in CAURAL. This included 100 patients in a 2nd line cohort, i.e. patients with T790M+ NSCLC who have progressed following an approved first-line EGFR-TKI treatment but who have not received further treatment and 250 patients in a 3rd line + cohort i.e. patients with T790M + NSCLC who have progressed following prior therapy with an approved EGFR-TKI and an additional anti-cancer treatment. Patients may have also received additional lines of treatment.

In order to randomize the planned 350 patients it was expected that an estimated 880 patients would have been screened. However due to the results of the AZD9291 plus MEDI4736 arm of the TATTON trial showing an increased incidence of Interstitial Lung Disease (ILD) in a subset of patients similar to those patients being studied in CAURAL, and in a population of patients receiving the combination as first line treatment, recruitment was terminated early in this trial. The Independent Data Monitoring Committee (IDMC) supported this decision. At the time of the decision not to restart recruitment, 60 patients were screened and 29 patients were randomized. In light of the early termination of recruitment, limited number of patients dosed in the study and the change in study scope, the IDMC, coordinating investigators and AstraZeneca have agreed that there is no further scope for IDMC to monitor the study.

All patients had documented radiological progression on EGFR-TKI treatment and on the last treatment administered prior to enrolling in the study. A mandatory biopsy was needed for central testing of T790M mutation status following confirmed disease progression on the most recent treatment regimen.

Patients had been initially randomized to receive either AZD9291 in combination with MEDI4736 or AZD9291 monotherapy. Depending on the treatment being received, the patients will be categorized as follows for the purpose of delineating the required study plan and assessments:

GROUP A - Patients on AZD9291 monotherapy

Group A includes patients continuing to receive AZD9291 monotherapy who were either randomised to receive AZD9291 monotherapy or were (ii) randomised to receive AZD9291 in combination with MEDI4736 but who have discontinued MEDI4736 and been followed up for 90 days post discontinuation of MEDI4736

Patients may continue dosing with the drug according to the protocol as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of a discontinuation criterion. These patients have no pre-scheduled visits until treatment

discontinuation (apart those needed for the drug accountability and dispensing) and will follow the normal clinical site approach while adhering to section 6.7 of this protocol.

GROUP B - Patients on MEDI4736 in combination with AZD9291 or MEDI4736 monotherapy

Group B includes patients receiving randomised to receive MEDI4736 and AZD9291 and are continuing to receive MEDI4736 either in combination with AZD9291 or as a monotherapy

Patients may continue treatment with MEDI4736 monotherapy or in combination with AZD9291 as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of a discontinuation criterion. Group B patients should follow the schedule / assessments specified in Table 2. Group B patients that discontinue MEDI4736 during the study can be switched to Group A and follow the AZD9291 Monotherapy assessment schedule following completion of the 90 day safety follow up.

All data collected before CSP Version 2.0 will be presented using descriptive statistics.

Objectives

Primary Objective:	**Outcome Measure:**
To investigate the safety and tolerability profile of AZD9291 in combination with MEDI4736.	Adverse events (graded by Common Terminology Criteria for Adverse Event (CTCAE v4)) Clinical chemistry, haematology and urinalysis Vital signs (pulse and blood pressure), Physical Examination, Weight Digital Electrocardiogram (ECG) Echocardiogram/Multi Gated Acquisition Scan (MUGA) (for Left Ventricular Ejection Fraction) WHO Performance Status

Exploratory Objective: To assess the safety and tolerability of AZD9291 as a single agent	**Outcome Measure:** **Pre- CSP Version 2.0** Adverse events (graded by Common terminology Criteria for Adverse Event CTCAEv4) Clinical chemistry, haematology and urinalysis Vital signs (pulse and blood pressure),Physical examination, Weight Centrally reviewed digital Electrocardiogram (ECG) Echocardiogram/Multi gated Acquisition Scan (MUGA) (for left ventricular Ejection fraction) WHO performance status **CSP Version 2.0** Serious Adverse events (graded by Common terminology Criteria for Adverse Event CTCAEv4)
To obtain a preliminary assessment of the efficacy of AZD9291 in combination with MEDI4736 and AZD9291 monotherapy	Objective Response Rate (ORR) Progression Free Survival (PFS) landmark at 6 and 12 months Overall Survival (OS) landmark at 12 months DoR DCR Tumour shrinkage using Investigator assessments according to RECIST 1.1
To assess the PK of AZD9291 as a single agent and in combination with MEDI4736.	Plasma concentrations of AZD9291 and metabolites AZ5104 and AZ7550.
To characterise the PK, immunogenicity and pharmacodynamics of MEDI4736 after single dosing and at steady state after multiple dosing when given intravenously to patients with EGFRm NSCLC in combination with AZD9291	Plasma concentrations of MEDI-4736 to characterise PK Blood samples for soluble PD-L1 and ADA to characterise pharmacodynamics and immunogenicity respectively.
To investigate the relationship of response and PFS in patients who are PD-L1 positive and those that are PD-L1 negative.	Retrospective evaluation of baseline PD-L1 expression in tumour (based on IHC assessment).
To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response AZD9291 as a single agent and in combination with MEDI4736 (i.e. absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers.	Correlation of polymorphisms with variation in Pharmacokinetics (PK), Pharmacodynamics (PD), safety or response observed in patients treated with AZD9291 as a single agent and in combination with MEDI4736.

To collect and store tumour samples and blood-based (plasma and serum) samples for potential exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or AZD9291 as a single agent and in combination with MEDI4736 (where response is defined broadly to include efficacy, tolerability or safety).	Collection of tumour and blood-based samples to include, but not be limited to, investigation of biomarkers such as EGFR mutations (T790M, L858R, etc). These samples may be shared with a diagnostic partner for development of a companion diagnostic if needed. The samples may also be used to investigate the relationship between PK and blood-borne biomarkers. Samples may be analysed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.

Note: Exploratory objective analyses may be reported separately from the main Clinical Study Report.

Target subject population

Male and female patients aged 18 years or over with EGFRm locally advanced or metastatic NSCLC (Stage IIIB-IV) centrally confirmed
T790M+ who have progressed following prior therapy with an approved EGFR-TKI agent. Patients may have also received additional lines of treatment.

Patients must have measurable disease (using Computer Tomography [CT]/Magnetic Resonance Imaging [MRI]) as defined by RECIST 1.1 guidelines, confirmation of histological or cytological NSCLC and WHO Performance Status of 0-1.

Duration of treatment

Patients may continue to receive either AZD9291 monotherapy or AZD9291 in combination with MEDI4736 or MEDI4736 monotherapy as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of a discontinuation criterion (see Section 3.7).

Patients on AZD9291 monotherapy will be seen as per their normal routine clinical care, or national label if approved in that Country (See Table 1). No clinical data will be collected for those patients who continue to receive AZD9291 as monotherapy, other than serious adverse events, outcomes of pregnancy, overdose and drug dispensing/accountability. Patients receiving only AZD9291, should be contacted 30 days after their last dose of AZD9291 to follow up any existing SAEs and monitor for new SAEs that may be related to IP.

Patients receiving AZD9291 + MEDI4736 combination therapy or MEDI4736 monotherapy should follow the study plan in Table 2. After discontinuation of MEDI4736, patients should complete their 90 day follow up. Patients continuing to receive AZD9291 as monotherapy following discontinuation of MEDI4736 and the 90 day follow up period will switch to the GROUP A study plan (Table 1).

Investigational product, dosage and mode of administration

AZD9291 (an oral, potent, irreversible EGFR-TKI selective for sensitizing (EGFRm) and T790M resistant mutations) and AZD9291 in combination with MEDI4736 [a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1] in NSCLC.

AZD9291 monotherapy will be dosed as a single agent (80 mg, orally, once daily) versus AZD9291 (80 mg, orally, once daily) in combination with MEDI4736 (10 mg/kg, IV) infusion q2w). A cycle of treatment is defined as 28 days and consists of either once daily AZD9291 monotherapy or once daily AZD9291 in combination with MEDI4736 infusion every 14 days (two MEDI4736 infusions per cycle).

Statistical methods

Patients were randomized to the trial in a 1:1 ratio (AZD9291+MEDI4736:AZD9291 alone) and stratified by previous lines of treatment (2nd or 3rd+) and ethnicity (Asian or Non-Asian).

The end of the study is defined as when the last patient receiving MEDI4736 (either as monotherapy or in combination with AZD9291) has permanently discontinued MEDI4736 and has completed their 90 day safety follow up

There will be two main summaries performed overall, unless there will be no patients continuing to receive MEDI4736 treatment after the DCO for the primary study summary in which case only primary summary will be performed. All summarise will be descriptive and no formal statistical analyses will be performed.

The primary summary will consist of safety and efficacy data dividing patients by randomised treatment. Safety and tolerability will be summarised for patients in safety analysis set and will include the following: adverse events graded by Common Terminology Criteria for Adverse Event (CTCAE v4), vital signs, laboratory tests, ECGs and WHO performance status. Efficacy summaries (PFS, ORR, DoR, DCR, OS) will be reported for patients in full analysis set showing the number of events at set intervals during follow up.

The final summaries will consist of data collected between the primary DCO and the time when last patient receiving MEDI4736 reaches the end of safety follow up. Patients will be described according to the following groups: Group A (patients receiving AZD9291 monotherapy either due to randomisation or due to discontinuing MEDI4736) and group B (patients receiving MEDI4736 either as combination or as monotherapy). Reduced data will be collected for Group A post primary DCO. Available safety data will be summarised for both groups and additional exploratory efficacy data will be reported for patients in Group B since the data will continue to be collected for group B patients post primary DCO.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatise
APF6	Proportion of patients alive and progression free at 6 months
APF12	Proportion of patients alive and progression free at 12 months
APF24	Proportion of patients alive and progression free at 24 months
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CK	Creatine kinase
CR	Complete Response
CRO	Clinical Research Organisation
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour DNA
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
DCR	Disease Control Rate
DILI	Drug induced liver injury
DLT	Dose limiting toxicity

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
DoR	Duration of Response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EGFR	Epidermal Growth Factor Receptor
EGFRm	Epidermal Growth Factor Receptor Mutation
EGFRis	Epidermal Growth Factor Receptor inhibitors
EGFR-TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
EGFR WT	Epidermal Growth Factor Receptor Wild Type
EMT	Epithelial-mesenchymal transition
ePRO	Electronic patient reported outcome
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FFPE	Formalin Fixed and Paraffin Embedded
FSH	Follicle-Stimulating Hormone
fT_3	Free triiodothyronine
fT_4	Free thyroxine
G719X	an in-frame amino acid (glycine (G)) deletion at position 719 in EGFR
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HDPE	High-Density-Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human immunodeficiency virus

Abbreviation or special term	Explanation
HL	Hy's Law
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMP	Investigational medicinal product
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.
IP	Investigational Product
irAE	Immune-related Adverse Event
irRC	Immune-related response criteria
irRECIST	Immune related RECIST
IV	Intravenous
KM	Kaplan-Meier
L858R	an amino acid substitution at position 858 in EGFR, from a leucine (L) to an arginine (R)
L861Q	an amino acid substitution at position 861 in EGFR, from a leucine (L) to a glutamine (Q)
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LH	Luteinizing Hormone
LIMS	Laboratory information management system
LMWH	Low Molecular Weight Heparin
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal antibody
MHC	Major histocompatibility complex

Abbreviation or special term	Explanation
MRI	Magnetic resonance imaging
MUGA	Multiple Gated Acquisition Scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-evaluable
NL	New lesions
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
NYHA	New York Heart Association
OAE	Other significant adverse events
OD	Once daily
ORR	Objective Response Rate
OS	Overall Survival
OS12	Proportion of patients alive at 12 months
OS24	Proportion of patients alive at 24 months
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival
PFS2	Time from randomization to second progression
PGx	Pharmacogenetic research
PHL	Potential Hys Law
PI	Principal Investigator
PK	Pharmacokinetic
PKPD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PTT	Partial thromboplastin time
q2w	Every 2 weeks

Abbreviation or special term	Explanation
QoL	Quality of Life
QT	Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart
QTc	The QT interval corrected for heart rate
QTcF	The QT interval corrected for heart rate (Fridericia's formula)
RPSFT	Rank Preserving Structural Failure Time
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria In Solid Tumours version 1.1
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable Disease
sPD-L1	Soluble Programmed Death Ligand 1
SRC	Safety Review Committee
T790M	an amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M)
T790M+	T790M mutation positive
TBL	Total bilirubin
TSH	Thyroid-stimulating hormone.
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WHO	World Health Organisation
WOCB	Women of Child Bearing Potential

1. INTRODUCTION

1.1 Disease background and unmet need – Non-small cell lung cancer

Lung cancer has been the most common cancer in the world for several decades. There were estimated 1.8 million new cases in 2012 (12.9% of the total). It is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total) (GLOBOCAN 2012). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC subjects already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC subjects who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005). Subjects presenting with unselected advanced NSCLC have a median overall survival of 10 to 12 months (Bonomi 2010).

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are now the established first-line therapy in subjects with NSCLC known to have activating mutations in EGFR (EGFRm) (NCCN 2012). Subjects with EGFRm NSCLC who receive EGFR-TKIs have a median overall survival of more than 2 years (Heuckmann et al 2012). The incidence of EGFRm NSCLC is approximately 10-15% and 30-40% of patients in the West and Asia, respectively. Second line therapy for EGFRm NSCLC is usually a platinum based chemotherapy. There is no global standard of care for third line therapy, but this may include chemotherapy or single agent therapy with an EGFR-TKI (Becker et al 2011, Langer et al 2012).

Selective inhibition of EGFR tyrosine kinase has demonstrated an objective response rate of approximately 70% in subjects with advanced NSCLC harbouring the sensitivity mutations [the most common of which are L858R and deletions in exon 19 (Ex19del)] (Oxnard and Miller 2010). The tumours initially respond to EGFR-TKIs, but subsequently develop resistance to therapy, with a median progression free survival of 8-13 months (Mok 2011, Rosell et al 2012, Sequist et al 2013). The emergence of a wild typeT790M mutation in subjects treated with an EGFR-TKI agent has been described as a major route of development of resistance to this class of therapy (Pao et al 2005, Kobayashi et al 2005) in up to approximately two-thirds (51-68%) of cases (Yu et al 2013, Oxnard et al 2011, Sun et al 2013, Arcila et al 2011, Kuiper et al 2014, Li et al 2014).

Treatment following progression on EGFR-TKI therapy is guided by patient performance status, symptoms, and extent of disease. In patients able to tolerate doublet chemotherapy, this would most often be the preferred second-line treatment. Following progression on doublet chemotherapy the only remaining options are re-challenge with EGFR-TKI or salvage single-agent chemotherapy or clinical trials. There is no global standard of care for later lines of therapy after failure of both EGFR-TKI therapy and chemotherapy (Langer et al 2012).

Patients who have progressed following platinum-containing chemotherapy

NCCN guidelines state response rates to systemic second-line therapy are generally <10%. In the subset of subjects whose tumours have failed prior platinum-containing doublet chemotherapy, studies in unselected patient populations (Shepherd et al 2000, Hanna et al 2004, Ramlau et al 2006, Kim et al 2008) highlight the low response rates and short PFS (median PFS approximately 2-3 months) expected with single-agent chemotherapy. These agents are also associated with a significant toxicity burden for the patient. Re-treatment with an EGFR-TKI (eg, switching to erlotinib following failure of gefitinib) provides similarly low response rates of around 10% and PFS in the range 1.7 to 6.2 months (Lee et al 2013, Watanabe et al 2011).

Patients who have not received platinum-containing chemotherapy after progressing on EGFR-TKI

Second-line platinum-based chemotherapy post EGFR-TKI for EGFRm NSCLC generally provides response rates in the range of 20 to 30% (Gridelli et al 2012, Goldberg et al 2012, Maemondo et al 2010, Wang et al 2012, Wu et al 2010). Although better than the response rates that can be expected with single-agent chemotherapy in later lines, they are generally of similarly short duration (median PFS approximately 3-6 months) and accompanied with significant toxicity burden including nausea, vomiting, bone marrow suppression resulting in high risk of infection and bleeding, alopecia, fatigue and peripheral neuropathy. Patients with stage IIIB / IV EGFR mutation-positive advanced NSCLC that progressed after first-line EGFR-TKI showed no statistically significant improvement in PFS with continuation of gefitinib in addition to cisplatin / pemetrexed versus chemotherapy alone (Mok et al 2014).

Patients who are eligible to receive PD1/PD-L1 therapy after progression on 1st line Therapies

Recently, nivolumab, a member of a new class of drugs targeting the PD1/PD-L1 interaction, has been approved for the treatment of squamous NSCLC in patients who progressed on prior chemotherapy (Rizvi et al 2015, Brahmer et al 2015). Compared to standard docetaxel, the activity of nivolumab was considered to be superior and the trial was stopped due to early efficacy. In the same year pembrolizumab, another drug targeting the PD-1/PD-L1 interaction, was also approved by the FDA for patients with metastatic NSCLC whose tumors express PD-L1. (Herbst et al 2015)

1.2 Background and rationale for conducting this study

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

B7-H1 (programmed cell death ligand 1 [PD-L1]). PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of subjects with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of subjects with tumors lacking PD-L1 (Mu et al 2011, Azuma et al 2014). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in subjects with cancer. Results of several non-clinical studies using mouse tumor models support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity (Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Zhang et al 2008).

Cancer evades immune recognition using several distinct mechanisms. Efficacious interventions to initiate and sustain an immune response will likely require a number of agents to simultaneously or sequentially trigger several immune mechanisms. Although master switches controlling various functions may exist, achievement of a curative immune response may ultimately demand the combined actions of several therapeutic components. Synergy occurs when drugs interact in ways that enhance the therapeutic effect.

Novel Emerging Therapies Targeting EGFR signaling and Immunotherapies in NSCLC

Recently, new chemical entities have been developed targeting specific mutations after patient's tumours progress on EGFR-TKIs. One such agent is AZD9291 which is an oral, potent, irreversible EGFR-TKI selective for sensitizing (EGFRm) and T790M resistance mutations with a significant selectivity margin over wild-type EGFR. Preliminary data from an ongoing phase I study (D5160C00001) in EGFRm/T790M+ NSCLC has demonstrated good evidence of efficacy, while treatment with AZD9291 has been well tolerated across a range of doses used (Ranson et al 2013).

Preliminary data from study D5160C00001 indicates that AZD9291 provides clinical benefit in patients with NSCLC harbouring the T790M resistance mutation following prior therapy with an EGFR-TKI (Jänne et al 2015).

Immunotherapies in NSCLC have also been recognized as effective novel treatments. For examples, MEDI4736 is such a novel biologic drug targeting PD-L1. In NSCLC subjects PD1 and PD-L1 inhibitors have shown activity in 2nd and 3rd line treated subjects, including ORR of about 10 to 30% (Garon et al 2014).

A relevant summary of the information for both, AZD9291 and MEDI4736, will be presented in this Clinical Study Protocol (CSP) (see below and Sections 1.3.1 and 1.3.2).

Rationale of Combining AZD9291 and MEDI4736

Originally the relationship of EGFR activation and evasion of immune responses in tumors was described in transformed keratinocytes (Pivarcsi et al 2007) Human keratinocyte-derived skin tumors down-regulate the expression of CCL27 through the activation of EGFR–Ras–

MAPK signaling pathways, which in turn promotes evasion from immune responses. *In vitro*, erlotinib increased CCL27 mRNA and protein production in keratinocytes. Increased expression of CCL27 was also observed in patients treated with EGFR-TKIs and present in TKI-related rashes. Reduction in CCL27 expression was associated with increases in T regulatory cells in tumours and promoting evasion of anti-tumour immune responses.

Recent studies further investigated the relationship of Programmed Death (PD)-1 expression and EGFR pathway activation. In murine models with EGFR-driven lung cancer, cytotoxic T cells were decreased and markers of T cell exhaustion were increased. Administering PD-1 antibodies to mice with EGFR-driven adenocarcinomas improved their survival. The survival was associated with enhanced effector T cell function and lowering the levels of tumor-promoting cytokines. PD-L1 expression was reduced by EGFR inhibitors in non-small cell lung cancer cell lines with activated EGFR. (Akbay et al 2013). The observation that PD-L1 expression is up-regulated by activation of the EGFR signaling and its mutation was recently corroborated (Chen et al 2015).

In a transgenic mouse model bearing EGFR mutations (L858R/T790m), the treatment with AZD9291 resulted in an increase in CD3+ T cells in tumours which led to tumour size reduction. This suggests that EGFR-TKIs can contribute to an immunological responses against NSCLC (PPD Yale University, personal communication and data on file).

In patients, PD-L1 expression was reported mainly in patients with adenocarcinoma histology and in the presence of EGFR mutations. Data in squamous cell carcinoma have not been published, but internal data suggest that such expression may range between 35 to 40% (AZ data on file).

Sensitivity to gefitinib or erlotinib was higher in PD-L1-positive vs PD-L1 negative patients after treatment with EGFR-TKIs (N=95). In the subset of 54 EGFR mutated subjects, TTP was significantly longer in PD-L1 positive than in PD-L1 negative subjects (D'Incecco et al 2014). Recently, response data of patients treated with pembrolizumab were reported, including 36 patients with a known EGFR mutation (Garon et al 2015). While the overall patient population had a response rate of 21%, patients with EGFR mutations had a response rate of 14%. Patients with PD-L1 expression (as defined by PD-L1 expression of more than 50% in tumour cells) had a response rate of 23%.

1.3 Description of clinical data to date for AZD9291 and MEDI4736

1.3.1 AZD9291

AZD9291 is an oral, potent, irreversible EGFR-TKI selective for sensitizing (EGFRm) and T790M resistance mutation with a significant selectivity margin against wild-type EGFR. As a result, AZD9291 can effectively block EGFR signaling both in EGFR single mutant cells with activating EGFR mutations and in double mutant cells bearing the resistance T790M mutation. AZD9291 was approved by the US FDA in November 2015 for the treatment of metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. Additional indications are currently under investigation (i.e. first line, adjuvant

settings in NSCLC). AZD9291 is also now approved in 45 countries, including Canada (30 June 2015), Taiwan (24 June 2015), South Korea (30 June 2015)

No dose-limiting toxicities were reported in any of the dose escalation cohorts (20, 40, 80, 160, and 240mg) and a non-tolerated dose has not been defined. Based on the totality of the safety, pharmacokinetic and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose. At this dose, CTCAE Grade ≥3 diarrhoea occurred in 1% (all grades 33%) and Grade ≥3 rash in 0% (all grades 32%) of patients.

In the advanced EGFRm NSCLC setting, subjects who have previously progressed on an EFGR TKI and have a T790M+ tumor have achieved promising efficacy with AZD9291; 54.2% 95% CI (40.8%, 67.3%) of subjects achieved a response, 91.5% 95% CI (81.3%, 97.2%) achieved disease control, medium duration of response of 12.4 months 95% CI (8.3, NC) and median PFS based on 38% maturity of data was 13.5 months 95% CI (8.3, NC) assessed by blinded independent central review (Jänne et al 2015).

The dose of AZD9291 in this study is 80 mg po once daily. This dose was selected from a review of all available safety, tolerability, pharmacokinetics and efficacy data from study D5160C00001, in patients with advanced EGFRm T790M+ NSCLC. Refer to Section 1.3.3 for further details.

Based on a latest data cut-off date of 1st October 2015, 1258 patients had been exposed to study treatment in the AZD9291 clinical program.

The following adverse reactions have been identified in clinical studies and the incidence using CIOMS frequency descriptors based on 411 EGFR mutation positive patients who received TAGRISSO at a dose of 80 mg daily is presented below:

Very common (≥10%): diarrhoea, rash, dry skin, paronychia, pruritus, and stomatitis-the majority of these adverse events have been mild or moderate. In addition findings based on test results presented as CTCAE grade shifts include platelet count decreased, leukocytes decreased and neutrophils decreased.

Common (>1% to <10%): Interstitial Lung Disease- fatal adverse events have been reported uncommonly

Uncommon (<1%): Keratitis; QTc interval prolongation >500ms

For further preclinical and clinical detail please refer to the AZD9291 Investigator's Brochure (IB).

1.3.2 MEDI4736

MEDI4736 is a human monoclonal antibody (mAb) of the immunoglobulin G 1 kappa subclass that inhibits the binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1, expressed on cancer cells and a subset of leukocytes, with the PD-1 (cluster of differentiation [CD] 279) and B7-1 (CD80) molecules on antigen-presenting cells and T-cells. By binding to PD-L1 on tumour cells, the mechanism of action of MEDI4736 includes stimulation of the patient's anti-tumour immune response.

MEDI4736 has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of 14 July 2014, 509 patients have been enrolled and treated in 10 ongoing clinical studies of MEDI4736 (5 employing MEDI4736 as monotherapy and 5 as combination therapy). Refer to the MEDI4736 Investigator's Brochure for a complete summary of non-clinical and clinical information; see Appendix G for guidance on management of MEDI4736-related toxicities.

Data presented at the European Society for Medical Oncology (ESMO) meeting 2014 related to 190 patients included in Study CD-ON-MEDI4736-1108 (cut-off date of 21 August, 2014) showed that MEDI4736 10 mg/kg q2w was well tolerated in the NSCLC subset of patients, with drug-related Grade ≥3 AEs reported in 3% of patients; drug-related AEs leading to discontinuation reported in 1% of patients; no drug-related colitis or hyperglycaemia of any grade; no Grade ≥3 pneumonitis reported; and no drug-related AEs leading to death reported (Antonia et al 2014b). No DLTs were observed up to a dose of 10 mg/kg q2w or 15 mg/kg q3w. Efficacy data on the NSCLC patients, 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 (25%; 12 complete response [CR]/PR; n=48) in patients with PD-L1 positive tumors defined as those with≥25% of tumor cells with membrane staining for PD-L1, compared to patients with PD-L1 negative tumors (10%; 7 CR/PR; n=74) (Antonia et al 2014b).

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

Data from study D4190C00006 (Phase 1 trial in NSCLC patients using the combination of MEDI4736 and tremelimumab), also show an approximately dose-proportional increase in PK exposure for MEDI4736 over the dose range of 3 to 20 mg/kg IV Q4W or Q2W. The observed MEDI4736 PK data from the combination study were well in line with the predicted monotherapy PK data (5th, median and 95th percentiles) for a Q4W regimen. A population PK model was developed using the data from Study CD-ON-MEDI4736-1108 (doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; Fairman et al 2014).

The important potential risks, based on the mechanism of action of MEDI4736 and related molecules, include immune-mediated reactions such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy or neurologic events. Additional important potential risks include infusion-related reactions, hypersensitivity, anaphylaxis or serious allergic reactions, serious infections, and immune complex disease.

Other mAbs targeting the PD-1/PD-L1 pathway are currently in clinical development. Among the most frequent AEs noted with treatment with these antibodies are fatigue, rash, diarrhea, and pruritus. Reported immune-mediated AEs of Grade ≥3 include pneumonitis, diarrhea, increased ALT, and increased AST. Other relevant risks include those associated with biological and immunotherapeutic agents, including infusion reactions and acute immunoglobulin E-mediated allergic reactions.

1.3.3 AZD9291 in combination with MEDI4736

As of September 2016, 34 patients have been exposed to AZD9291 in combination with MEDI4736 as part of the TATTON study (D5160C00006). The TATTON trial is a Phase I, multi-arm open label study assessing the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of AZD9291 in combination with various novel therapeutics. The study consists of two parts; Part A: Dose escalation and Part B: Dose expansion. Two dose levels of MEDI4736 have been explored in Part A of the study in patients who had received at least one prior EGFR TKI regimen for advanced NSCLC; 3mg/kg IV every 2 weeks (10 patients dosed) and 10mg/kg IV every 2 weeks (13 patients dosed). In part B of the study, 11 EGFR TKI treatment naïve patients have received the combination with MEDI4736 10mg/kg IV every 2 weeks. Safety data relating to patients receiving MEDI4736 in combination with 80mg po AZD9291 has been reviewed by an independent Safety Review Committee (SRC) on an ongoing basis throughout the study.

Osimertinib, at a dose of 80 mg daily, in combination with durvalumab at dose levels of 3.0 mg/kg and 10.0 mg/kg every 2 weeks, were declared tolerated by the SRC in the Phase I part of TATTON. One dose limiting toxicity (DLT) of grade 3 neutropenia was reported for the combination of osimertinib 80 mg once daily and durvalumab 10 mg/kg once every 2 weeks. Other than ILD cases (see below), the most common AEs for the combination of osimertinib and durvalumab were diarrhoea, vomiting, anemia, constipation, cough and nausea.

In the TATTON study as of 18th September 2015, ILD-like events were reported in 6/23 patients with pre-treated EGFRm+ NSCLC receiving the combination (2 on MEDI4736

3mg/kg q 2w plus AZD9291 and 4 on MEDI4736 10mg/kg q2w plus AZD9291). Of these 6 events, 3 events were considered SAEs and 2 events were CTCAE Grade 3 or 4. In addition ILD-like events were reported in 5/11 patients in Part B of the TATTON study. Of these 5 events, 4 events were considered SAEs and 3 events were CTCAE Grade 3 or 4. .

At the time of the September 18th 2015 data cut off, the TATTON study had shown an incidence rate of 32% for ILD-like events with the combination of AZD9291 and MEDI4736 (11 events in 34 patients); this is compared with an overall frequency of pneumonitis (including both non-serious and serious cases) of around 2% for MEDI4736 monotherapy across all doses and indications and an overall frequency of pneumonitis/ILD of 2.4% for AZD9291 monotherapy (see Section 6.6.5 of the AZD9291 investigator brochure). None of the ILD-like events reported in the TATTON study have been fatal. While there was an increased incidence in the ILD reporting rate for the MEDI4736 + AZD9291 combination, there was no apparent increase in severity, compared with either drug as a monotherapy.

As of September 2016, a further 2 patients had ILD-like events in PART B of TATTON (One CTCAE Grade 1 and one CTCAE Grade 2 event). Thus the incidence rate of ILD-like events in the TATTON study is 6/23=26% in PART A, 7/11 =64% in PART B and 13/34=38% overall.

In September 2015 enrolment of new patients into the AZD9291 and MEDI4736 combination arm of TATTON and the CAURAL study was suspended due to these reports of ILD-like events in TATTON and it has not been restarted since then in either of the studies. In the TATTON study, of 21 evaluable pts from Part A, 12 had a partial response (PR, 9 confirmed) and 9 had stable disease (SD). Of 10 evaluable pts from Part B, 8 had a PR (7 confirmed) and 2 had SD. (Ahn et al 2016)

In this study (CAURAL), 14 patients were originally randomised to receive AZD9291 in combination with MEDI4736. When patients were re-consented in October 2015, seven patients discontinued MEDI4736 and continued with AZD9291 monotherapy of whom five patients are continuing to receive AZD9291 monotherapy as of November 2016. Seven patients continued with combination treatment, four of whom were continuing to receive combination therapy as of November 2016. Based on preliminary information, one patient in CAURAL randomised into the AZD9291 & MEDI4736 combination arm (MEDI4736 was discontinued after 1 cycle due to patient decision), developed a serious adverse event of CTC grade 2 ILD 63 days after commencing randomised treatment. AZD9291 was discontinued. The investigator considered this event related to AZD9291. The patient died 95 days later; the death was deemed not to be related to the ILD which was still ongoing at the time of the patient's death. 15 patients were randomised to receive AZD9291 monotherapy of whom 12 remain on therapy as of November 2016. There have been no reports of ILD-like events.

1.4 Rationale for study design, doses and control groups

EGFR-TKIs are the established first-line therapy in patients with NSCLC possessing activating mutations in EGFR (EGFRm) (NCCN 2012). The presence of activating EGFRm

in patients with NSCLC tumours confers sensitivity to the EGFR-TKI class of drugs in a high percentage of patients. However, the response to this class of agents is eventually lost due to development of a variety of resistance mechanisms, with the EGFR T790M mutation being a major route of development of resistance to this class of therapy. Additional routes of acquired resistance include activation of a bypass signaling pathway (such as MET amplification, human epidermal growth factor receptor 2 (HER2) upregulation or RAS mutations), histological transformation to small cell lung cancer and epithelial-mesenchymal transition (EMT) (Ohashi et al 2012, Chong and Jänne 2013).

Treatment following progression on EGFR-TKI therapy is guided by patient performance status, symptoms, and extent of disease. In such patients, current treatment options for this selected patient population are generally limited to chemotherapy or clinical trials (Langer et al 2012). There is thus a considerable unmet clinical need for well-tolerated novel therapeutic options, including novel-novel combinations, for patients with EGFRm NSCLC following progression on EGFR-TKI therapy (across lines).

AZD9291 is an oral, potent, irreversible EGFR-TKI selective for sensitizing (EGFRm) and T790M resistance mutations with margin over wild-type EGFR.

The dose of AZD9291 in this study is 80 mg once daily. This dose was selected from a review of all available safety, tolerability, pharmacokinetics and efficacy data from study D5160C00001, in patients with advanced EGFRm NSCLC. No DLTs have been reported at any dose level in the escalation cohorts during the 21-day DLT evaluation period. As of August 2014, AZD9291 had been administered as a capsule formulation across the 20 to 240 mg once daily dose range in more than 253 patients with advanced NSCLC who have progressed following prior therapy with an EGFR-TKI: 20 mg (n=21), 40 mg (n=58), 80 mg (n=90), 160 mg (n=63), and 240 mg (n=21). Emerging efficacy data have demonstrated durable objective responses from the starting dose level of 20 mg once daily (Ranson et al 2013, Yang et al 2014). The Objective Response Rate (ORR) in relapsed/refractory T790M+ patients was 61% (Yang et al 2014). The Phase II dose for the T790M+ clinical programme has been selected as 80 mg once daily based on both the activity in patients with T790M+ NSCLC and the low incidence of toxicity (Jänne et al 2014, Yang et al 2014). The selected 80 mg dose is 4 fold higher than the minimum efficacious dose tested in study D5160C00001, whilst still being one third of the maximum dose level investigated (240 mg).

The toxicity profile of AZD9291 makes rational combinations with potentially synergistic targeted therapies feasible at biologically active doses (Oxnard et al 2015). The 80 mg daily dose is considered to provide the optimum risk/benefit ratio in this patient population and will therefore be used in this Phase III study.

Currently, AZD9291 is approved in 45 countries, including Canada (30 June 2015), Taiwan (24 June 2015), South Korea (30 June 2015) for the treatment of metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy.

The CAURAL study proposes to use AZD9291 as the control arm.

At the time of writing the original protocol, there were no approved therapies that effectively addressed acquired resistance to EGFR-TKI therapy as a result of the EGFR T790M mutation, which is the most common mechanism of resistance to this class of drug. Available treatment options had limited clinical effectiveness, regardless of mutational status. In patients able to tolerate platinum-containing doublet chemotherapy, this would most often be the preferred second-line treatment. Second-line platinum-based chemotherapy post EGFR-TKI for EGFRm NSCLC generally provides response rates in the range of 20 to 30% (Gridelli et al 2012, Goldberg et al 2012, Maemondo et al 2010, Wang et al 2012, Wu et al 2010, Mok et al ESMO 2015). In the subset of patients whose tumours have failed prior platinum-containing doublet chemotherapy, studies in unselected patient populations highlight the low response rates (approximately 10%) and short PFS (median PFS approximately 2-3 months) expected with single-agent chemotherapy such as docetaxel, or pemetrexed (Shepherd et al 2000, Fossella et al 2000, Hanna et al 2004). Lastly, Re-treatment with an EGFR-TKI (eg, switching to erlotinib following failure of gefitinib or re-treatment with the same EGFR-TKI after a period off drug) provides low response rates of around 10% and PFS in a similar range to that of single-agent chemotherapy (Lee et al 2013).

At the recommended daily dose of 80mg once daily , the dose used in the CAURAL study , the BICR-assessed confirmed ORR in pooled phase 2 studies was 66% (95% CI 61,71) and the median duration of response was NE months (95% CI 8.3,NE) The median progression-free survival was 9.7 months (95% CI 8.3,NE). These data indicate clear improvements of AZD9291 over the benefit offered by currently available therapeutic options.

As neither AZD9291, nor any other therapy approved in the T790M mutation-positive NSCLC population, will be curative in intent, there will remain an unmet medical need. The CAURAL study was designed not only with the future standard of care in mind, but also with the intent to address the emergent unmet medical need which will exist at that time.

EGFRm lung cancer in mice has been shown to be PD-L1 positive, and forced expression of mutant EGFR in human tumour cell lines has been shown to drive increased PD-L1 expression (Akbay et al 2013). In addition epithelial-mesenchymal transition (EMT), a driver of resistance to EGFR inhibitors (EGFRIs), correlates with increased expression of PD-L1 on tumour cells in vitro.

This suggests that there may be overlap in the patient segment that would benefit from both therapies.

A combination of an immune mediated therapy, such as MEDI4736, with a targeted therapy such as AZD9291 in these subjects has the potential to help overcome resistance since, in contrast to the rapid resistance seen with targeted therapies, responses to immune mediated therapies such as anti-CTLA-4 and anti-PD-L1 have generally been durable (Ott et al 2013). In addition, gefitinib and other EGFR inhibitors (EGFRis), have shown a number of immunomodulatory properties that could be considered beneficial to the activity of MEDI4736. Specifically, in vitro studies have shown that EGFRis can enhance the cytotoxic activity of NK cells to human lung cancer cells (He et al 2013), augment the expression of

class I and class II MHC molecules (Pollack et al 2011), and drive pro-inflammatory chemokine release (Mascia et al 2003).

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 mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile (Brahmer et al 2012, Topalian et al 2012).

A combination of an immune mediated therapy, such as MEDI4736 (currently in phase III), with a targeted therapy such as AZD9291 also has the potential to help overcome mechanisms of EGFR-TKI resistance. The immune system is capable of identifying and eliminating cancerous cells, but anti-tumour immune response is often held in check by immunosuppressive mechanisms. One such suppressive mechanism is expression of PD-L1 on the surface of tumour cells (Keir et al 2008). MEDI4736 is a human IgG1κ MAb directed against human PD-L1. Preclinically expression of mutant EGFR in human tumour cell lines has been shown to drive increased PD-L1 expression (Akbay et al 2013). In addition EMT, a driver of resistance to EGFR inhibitors (EGFRIs), correlates with increased expression of PD-L1 on tumour cells in vitro.

Preliminary evidence in support of this hypothesis is provided by emerging data from a study of this combination in NSCLC (Antonia et al 2014a) and data from other tumors and agents, eg, the combination of ipilimumab and nivolumab in melanoma, which has been shown to result in higher ORRs and 1-year survival compared with either agent alone, regardless of PD-L1 expression status (Wolchok et al 2013).

1.5 Benefit/risk and ethical assessment

In the setting of advanced NSCLC post EGFR-TKI treatment failure that has been chosen for initial combination efficacy and tolerability study with AZD9291 plus MEDI4736, prolonged survival rates are very low (~16 months for second line therapy, ~10 months for third line therapy) and there is a huge unmet clinical need for novel therapeutic agents for patients who have developed the resistance mutation. At the time of writing the original protocol, and prior to approval of AZD9291, there were no approved therapies for this specific NSCLC patient population. Response rates with single-agent chemotherapy for third- and later-line treatment are generally <10%, and short-lived (median PFS 2-3 months). These agents are also associated with a significant toxicity burden for the patient. Response rates with second-line platinum-based doublet chemotherapy post EGFR-TKI for EGFRm NSCLC are generally in the range of 20 to 30% with limited PFS (approximately 3-6 months). There is a significant toxicity burden associated with doublet chemotherapy (that includes nausea, vomiting, bone marrow suppression resulting in high risk of infection and bleeding, alopecia, fatigue and peripheral neuropathy).

As described in section 1.4, a combination of MEDI4736, an immune mediated therapy, with AZD9291, a targeted therapy, has the potential to help overcome mechanisms of EGFR TKI resistance.

Preliminary efficacy data from study D5160C00001 suggest clinicial benefit may be provided to patients with EGFRm NSCLC receiving AZD9291 administered as monotherapy. The biological hypotheses and non-clinical data from the proposed combination of agents suggest that combination therapy may provide additional clinical benefit in patients with NSCLC tumours driven via the EGFR pathway and may, in addition, delay the development of resistance to AZD9291. Please refer to Section 1.3.1.

The non-clinical safety profile for each agent has not identified any risks that would preclude investigation in this patient setting as monotherapy. However, the combination of two novel investigational agents may potentially result in synergistic toxicity or a novel toxicity which could be associated only with the combination.

Emerging safety data from the TATTON study (D5160C00006) in October 2015 identified a higher frequency of ILD-like events occurring in patients receiving the combination of AZD9291 with MEDI4736 compared to the monotherapy profile of each individual agent. As such, enrolment of new patients into this study is now closed, but patients who had tolerated the combination were permitted to continue to receive the combination or discontinue MEDI4736 or both agents once they have been re-consented regarding these safety findings.

The risk benefit assessment of this approach is considered appropriate given that:

(a) None of the ILD-like events reported in the TATTON study, or the single event that has occurred to date in CAURAL have been fatal. While there was an increased incidence in the ILD reporting rate for the MEDI4736 + AZD9291 combination in TATTON, there was no apparent increase in severity, compared with either drug as a monotherapy.

(b) Patients receiving AZD9291 in combination with MEDI4736 will continue to be closely monitored whilst receiving MEDI4736 and for 90 days post discontinuation of MEDI4736.

(c) Patients that continue to receive MEDI4736 either in combination with AZD9291 or as monotherapy may only do so if they are receiving clinical benefit from therapy, as judged by the investigator.

(d) Whilst AZD9291 monotherapy is an effective therapy for patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have received prior EGFR TKI therapy, i.e. the population of patients in CAURAL, patients will typically experience disease progression after an average of ~10 months. Thus there remains a significant unmet medical need that the combination of AZD9291 and MEDI4736 has the potential to address.

(e) The data collected in this study has the potential to inform future developments in the area of immunotherapy/EGFR TKI combination therapy for the management of patients with EGFRm+ T790M NSCLC

1.6 Study Design

This trial was initially designed as a phase III, multi-centre, open label, randomized study to assess the efficacy and safety of AZD9291 (80 mg, orally, once daily) in combination with MEDI4736 [10 mg/kg (IV) infusion every 2 weeks (q2w)] versus AZD9291 monotherapy (80 mg, orally, once daily) in patients with a confirmed diagnosis of Epidermal Growth Factor Receptor (EGFR) T790M mutation positive (hereafter referred to as EGFR T790M+) NSCLC (Stage IIIB-IV), who have progressed following prior therapy with an approved Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) agent.

Three hundred fifty patients were planned to be enrolled in CAURAL. This included 100 patients in a 2nd line cohort, i.e. patients with T790M+ NSCLC who have progressed following an approved first-line EGFR-TKI treatment but who have not received further treatment and 250 patients in a 3rd line + cohort i.e. patients with T790M + NSCLC who have progressed following prior therapy with an approved EGFR-TKI and an additional anti-cancer treatment. Patients in this 3rd line + cohort may have also received additional lines of treatment.

In order to randomize the planned 350 patients it was expected that an estimated 880 patients would have been screened. However due to the results of the AZD9291/ MEDI4736 arm of the TATTON trial showing an increased incidence of Interstitial Lung Disease (ILD) in a subset of patients similar to those patients recruited to CAURAL, recruitment was terminated early in this trial. The IDMC supported this decision. At the time of the decision to not restart recruitment, 60 patients were screened and 29 patients were randomized.In light of the early termination of recruitment, a limited number of patients dosed in the study and the change in study scope, the IDMC, coordinating investigators and AstraZeneca have agreed that there is no further scope for IDMC to monitor the study.

Patients had been initially randomized to receive either AZD9291 in combination with MEDI4736 or AZD9291 monotherapy. Depending on the treatment being received, patients will be categorized as follows for the purpose of delineating the required study plan and assessments:

GROUP A - Patients on AZD9291 monotherapy

Group A includes patients continuing to receive AZD9291 monotherapy who were either randomised to receive AZD9291 monotherapy or were (ii) randomised to receive AZD9291 in combination with MEDI4736 but who have discontinued MEDI4736 and been followed up for 90 days post discontinuation of MEDI4736

Patient may continue dosing with the drug according to the protocol as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of a discontinuation criterion. These patients have no pre-scheduled visits until treatment discontinuation (apart those needed for the drug accountability and dispensing) and will follow the normal clinical site approach while adhering to section 6.7 of this protocol. See Table 1.

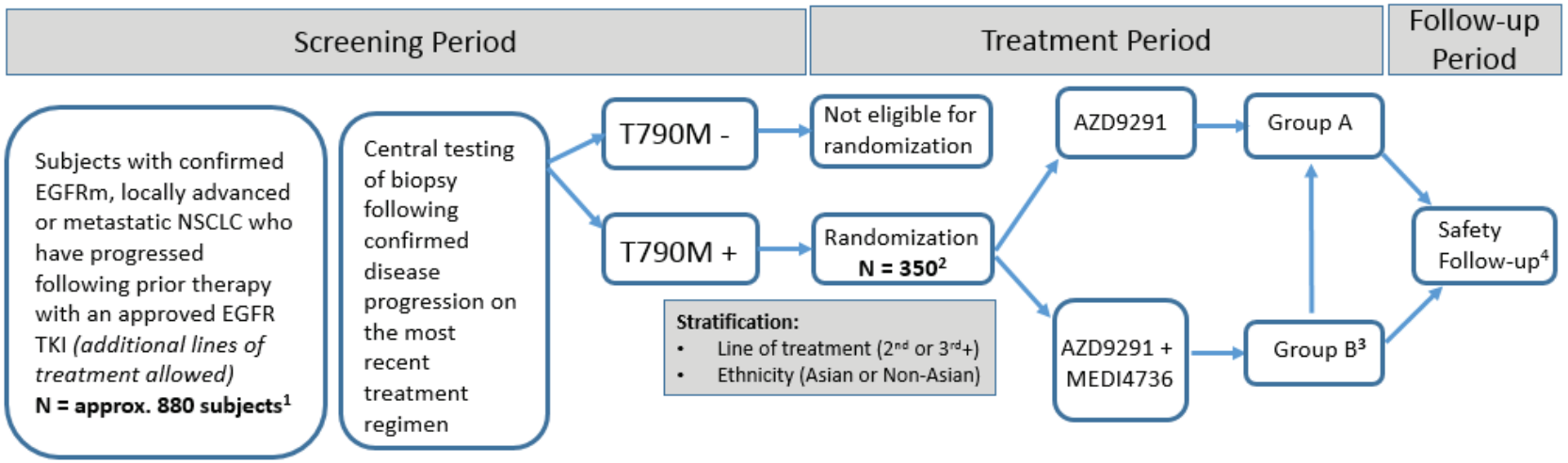
GROUP B - Patients on MEDI4736 in combination with AZD9291 or MEDI4736 monotherapy

Group B includes patients receiving randomised to receive MEDI4736 and AZD9291 and are continuing to receive MEDI4736 either in combination with AZD9291 or as a monotherapy

Patients may continue treatment with MEDI4736 in combination with AZD9291 or continue on monotherapy MEDI4736 as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of a discontinuation criterion as per Table 2. Patients being treated with the combination can be switched to the GROUP A assessment schedule following discontinuation of MEDI4736, continuation of AZD9291 monotherapy and completion of the 90 day follow up detailed in Table 3. (See section 4.3) Patients on MEDI4736 monotherapy cannot be switched to Group A and restart AZD9291 treatment.

A schematic diagram of the overall study flow is shown in Figure 1

Figure 1 Study Flow



1 Due to termination of recruitment, final screened patients = 60

2 Due to termination of recruitment, final randomized patients = 29

3 Patients receiving the combination treatment who discontinue MEDI4736 may be switched to Group A following the completion of the required safety follow up period

4 Patients receiving only AZD9291 at the time of treatment discontinuation should be contacted 30 days after their last dose to follow up on any existing SAEs and monitor for new SAEs that may be related to the IP.

Patients who discontinue the combination treatment (AZD9291 + MEDI4736) or discontinue AZD9291 <90 days after discontinuing MEDI4736 will complete a 90 day safety follow up period

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To investigate the safety and tolerability profile of AZD9291 in combination with MEDI4736.	Adverse events (graded by Common Terminology Criteria for Adverse Event (CTCAE v4)) Clinical chemistry, haematology and urinalysis Vital signs (pulse and blood pressure), Physical Examination, Weight Digital Electrocardiogram (ECG) Echocardiogram/Multi Gated Acquisition Scan (MUGA) (for Left Ventricular Ejection Fraction) WHO Performance Status

2.2 Exploratory Objectives

Exploratory Objective:	Outcome Measure :
To assess the safety and tolerability of AZD9291 as a single agent	**Pre- CSP Version 2.0** Adverse events (graded by Common terminology Criteria for Adverse Event CTCAEv4) Clinical chemistry, haematology and urinalysis Vital signs (pulse and blood pressure),Physical examination, Weight Centrally reviewed digital Electrocardiogram (ECG) Echocardiogram/Multi gated Acquisition Scan (MUGA) (for left ventricular Ejection fraction) WHO performance status **CSP Version 2.0** Serious Adverse events (graded by Common terminology Criteria for Adverse Event CTCAEv4)
To obtain a preliminary assessment of the efficacy of AZD9291 in combination with MEDI4736 and AZD9291 monotherapy	Objective Response Rate (ORR) Progression Free Survival (PFS) landmark at 6 and 12 months Overall Survival (OS) landmark at 12 months DoR DCR Tumour shrinkage using Investigator assessments according to RECIST 1.1
To assess the PK of AZD9291 as a single agent and in combination with MEDI4736.	Plasma concentrations of AZD9291 and metabolites AZ5104 and AZ7550.
To investigate the relationship of response and PFS in patients who are PD-L1 positive and those that are PD-L1 negative.	Retrospective evaluation of baseline PD-L1 expression in tumour (based on IHC assessment).
To characterise the PK, immunogenicity and pharmacodynamics of MEDI4736 after single dosing and at steady state after multiple dosing when given intravenously to patients with EGFRm NSCLC in combination with AZD9291	Plasma concentrations of MEDI-4736 to characterise PK Blood samples for soluble PD-L1 and ADA to characterise pharmacodynamics and immunogenicity respectively.

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response AZD9291 as a single agent and in combination with MEDI4736 (i.e. absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to/development of cancers.	Correlation of polymorphisms with variation in Pharmacokinetics (PK), Pharmacodynamics (PD), safety or response observed in patients treated with AZD9291 as a single agent and in combination with MEDI4736.
To collect and store tumour samples and blood-based (plasma and serum) samples for potential exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or AZD9291 as a single agent and in combination with MEDI4736 (where response is defined broadly to include efficacy, tolerability or safety).	Collection of tumour and blood-based samples to include, but not be limited to, investigation of biomarkers such as EGFR mutations (T790M, L858R, etc). These samples may be shared with a diagnostic partner for development of a companion diagnostic if needed. The samples may also be used to investigate the relationship between PK and blood-borne biomarkers. Samples may be analysed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.

Note: Exploratory objective analyses may be reported separately from the main Clinical Study Report.

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

Recruitment into the CAURAL study was halted as of September 28th 2015 and will not be restarted as recruitment is now terminated.

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

3.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures, sampling and analyses. *If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.*

2. Male or female aged at least 18 years and older. Patients from Japan should be aged at least 20 years.

3. Histological or cytological confirmation diagnosis of NSCLC.

4. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy

5. Documented EGFR mutation (at any time since the initial diagnosis of NSCLC) known to be associated with EGFR-TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q).

6. Radiological documentation of disease progression while on a previous continuous treatment with an approved EGFR-TKI (eg, gefitinib, erlotinib or afatinib). In addition other lines of therapy may have been given. All patients must have documented radiological progression on the last treatment administered prior to enrolling in the study.

7. Patients must have central lab confirmation of tumour T790M status from a biopsy taken after disease progression on the most recent treatment regimen. Only patients with a T790M positive status central test result will be included in the study, see Section 4.1.

8. At least one lesion, not previously irradiated and not biopsied during the screening period, 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 computerised tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements per RECIST v1.1 guidelines. **If only one measurable lesion exists, it is acceptable to be used as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.**

9. World Health Organisation (WHO) performance status 0-1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks.

10. Females should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to start of dosing (if of child-bearing potential) or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
    - Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
    - Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution
    - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

11. Male patients should be willing to use barrier contraception (see Restrictions, Section 3.6).

12. For inclusion in the **optional genetic research**: Patients must provide informed consent for genetic research. *If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.*

3.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

2. Intervention with any of the following:
   - Treatment with an EGFR-TKI within approximately 5x half-life (eg, within 8 days for erlotinib, gefitinib or afatanib, within 10 days for dacomitinib) of the first dose of study treatment. *If sufficient washout time has not occurred due to schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug related adverse events could be agreed upon by AstraZeneca and the Investigator.*
   - Any cytotoxic chemotherapy, investigational agents or other anticancer drugs for the treatment of advanced NSCLC from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment.
   - Patients currently receiving (or unable to stop use at least 1 week (3 weeks for inducers) prior to receiving the first dose of AZD9291) medications or herbal supplements known to be potent inhibitors or inducers of CYP3A4 (Appendix E).
   - Previous treatment with AZD9291 or other agents specifically targeted against EGFR T790M mutation positive NSCLC (eg rociletinib [CO-1686]).
   - Prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months of starting
   - 1st EGFR-TKI treatment.
   - Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of randomization. Radiotherapy with a limited field of radiation for palliation >1 week of the first dose of study treatment is allowed.
   - Major surgical procedure, (excluding placement of vascular access) or significant traumatic injury within 4 weeks of the first dose of study treatment, or have an anticipated need for major surgery during the study.
   - No prior exposure to immune-mediated therapy including, but not limited to, other anti CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.

3. Current or prior use of immunosuppressive medication within 14 days before the first dose of MEDI4736. The following are exceptions to this criterion:

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

4. With the exception of alopecia and grade 2 prior platinum-therapy related neuropathy, any unresolved toxicities from prior therapy and/or pre-study biopsies greater than CTCAE grade 1 at the time of starting study treatment.

5. History of active primary immunodeficiency.

6. Current leptomeningeal metastases or spinal cord compression. Brain metastases are only permitted if asymptomatic and stable (not requiring steroids for at least 4 weeks prior to start of study treatment).

7. 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 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.

8. Any of the following cardiac criteria:
   - Mean resting corrected QT interval (QTcF) > 470 msec obtained from 3 ECG readings
   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250msec.
   - Any factors that increase the risk of QTcF prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval.

9. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD9291

10. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.

11. History of another primary malignancy except for:
    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)

12. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis with the exception of diverticulosis, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc) within the past 3 years prior to the start of treatment.

    The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment

13. History of organ transplant that requires use of 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 (TNF-α) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

14. Known history of clinical diagnosis of tuberculosis

15. Receipt of live, attenuated vaccine within 30 days prior to the first dose of MEDI4736.

16. History of hypersensitivity to active or inactive excipients of AZD9291 or MEDI4736 or drugs with a similar chemical structure or class to these agents.

17. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

18. Women who are breast feeding.

19. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
    - Absolute neutrophil count < 1.5 x 10^9/L
    - Platelet count < 100 x 10^9/L
    - Haemoglobin < 90 g/L

- Alanine aminotransferase > 2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
- Aspartate aminotransferase > 2.5 times ULN if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
- Total bilirubin > 1.5 times ULN. Total bilirubin >3 times the ULN in patients with documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or in the presence of liver metastases
- Creatinine >1.5 times ULN concurrent with creatinine clearance < 50 ml/min (measured or calculated by Cockcroft and Gault equation), confirmation of creatinine clearance is only required when creatinine is > 1.5 times ULN.

  Males:

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

  Females:

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

In addition, the following is considered a criterion for exclusion from the exploratory genetic research:

20. Previous allogeneic bone marrow transplant.

21. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.3.

3.3 Subject enrolment and randomization

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

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

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed. Informed consent of study procedures may be obtained prior to the 28-day screening window in order to permit tumour biopsy sample acquisition which must be analyzed prior to randomization.

2. Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS in the following format (ECCNN8XX: CC being the country code, NN being the center number, and 8XX being the patient enrolment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

3. Obtain tumour sample and send for T790M testing. The tumour biopsy sample may be obtained and sent for T790M status evaluation prior to the 28-day screening window in order to permit analysis and reporting prior to randomization.

4. Determine patient eligibility. See Sections 3.1 and 3.2.

5. Obtain signed informed consent for optional genetic research and biological samples (if applicable).

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

1. Obtain a unique randomization number via the IVRS/IWRS. The system will randomize the eligible patients to one of the two treatment groups. The number of previous lines of treatment and ethnicity (Asian or Non-Asian) must be received by the IVRS/IWRS prior to randomization for stratification.

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

If a patient is re-screened, a new E-code must be assigned. Any repeated tests and/or procedures will be performed as per documented local standards. Patients will reconfirm their consent to participate in the study by resigning and dating their original consent form(s), next to their initial signature and date. A sample with a valid mutation test result cannot be re-tested. A rescreened patient can provide tissue from a new biopsy sample for mutation testing, if required.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

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

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from

treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The actual treatment given to patients will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.
One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group.

Eligible patients will be centrally randomized to receive either AZD9291 monotherapy (80 mg, orally, once daily) versus AZD9291 (80 mg, orally, once daily) in combination with MEDI4736 (10 mg/kg (IV) infusion q2w).

Patients have been stratified at randomization based on previous lines of treatment (2nd or 3rd+) and ethnicity (Asian or Non-Asian).

Investigators will have the option of:

- Continue treating patients with AZD92921 monotherapy as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of a discontinuation criterion (Section 3.7). These patients will be part of GROUP A as defined within section 1.6. These patients have no pre-scheduled visits and no clinical data will be collected for those patients who continue to receive AZD9291 as monotherapy, other than serious adverse events, outcomes of pregnancy and drug dispensing/accountability. See Table 1. Patients receiving only AZD9291, should be contacted 30 days after their last dose of AZD9291 to follow up any existing SAEs and monitor for new SAEs that may be related to IP.

- Or continue treating patients with MEDI4736 in combination with AZD9291 or MEDI4736 monotherapy as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of a discontinuation criterion see (Section 3.7).These patients will be part of GROUP B and will follow the study plan detailed in Table 2. Patient in the combination arm can discontinue MEDI4736 and continue on AZD9291 monotherapy. These patients will be switched to GROUP A and follow the assessment schedule as per Table 1 after the completion of their 90 day follow up (See section 4.3). Patients on MEDI4736 monotherapy cannot be switched to Group A and restart AZD9291 treatment.

3.6 Restrictions

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing MEDI4736 and up to 6 weeks after discontinuing AZD9291. Acceptable methods of contraception include total

sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions, Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)], copperbanded intra-uterine devices and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners during the trial and for a washout period of 4 months. Patients should avoid procreation for 4 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuing study treatment. If male patients wish to father children during the study they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

3. Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of AZD9291. All concomitant medications should be captured on the eCRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix E).

4. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above) should be maintained on it throughout the study period. A patient taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring, and on washout periods is provided in Appendix E.

   Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

5. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with AZD9291 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events, they must discontinue wearing their contact lenses until at least one week after

treatment with AZD9291 is permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after AZD9291 has been permanently discontinued. Patient should consult the clinic promptly if they have any concerns.

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

3.7 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment(s), without prejudice to further treatment
- Adverse Event
- For Group B patients: Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Appendix G)
- Pregnancy or intent to become pregnant
- Severe non-compliance with the study protocol as judged by the Investigator and/or AstraZeneca
- Subject incorrectly initiated on study treatment
- Corneal ulceration
- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia
- Objective disease progression or subject is no longer receiving clinical benefit
- Initiation of alternative anticancer therapy including another investigational agent
- Lost to follow-up

3.7.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product(s) or withdraw from the study (i.e., investigational product and assessments) without prejudice to further treatment. A subject that decides to discontinue investigational product(s) will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed

by an Investigator(s). Adverse events will be followed up (See Section 6.3); electronic questionnaire devices (e.g., for patient reported outcomes) and all unused study drug should be returned by the subject or representative (e.g. caretaker, family member).

After discontinuation of AZD9291 + MEDI4736 combination therapy or MEDI4736 monotherapy, Group B patients should complete the 90 day follow up. Group A patients receiving AZD9291 monotherapy, should be contacted 30 days after their last dose of AZD9291 to follow up any existing SAEs and monitor for new SAEs that may be related to IP. See section 4.3

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

If a subject is withdrawn from study, see Section 3.8.

3.8 Criteria for withdrawal

The term withdrawal from the study refers to both discontinuation from study treatment and study assessments. Withdrawn patients will not be replaced.

3.8.1 Screen failures

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

3.8.2 Withdrawal of the informed consent

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

Patients may withdraw from any aspect of the voluntary research (see Sections 3.8, 5.5 and 5.6.1.3) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The patient will return electronic PRO (ePRO) device and unused study drug.

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

3.9 Discontinuation of the study

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

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

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

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Group A: Study Plan detailing the procedures for the AZD9291 monotherapy arm Safety Monitoring

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	**Assessments**	**Treatment Discontinuation**	**AZD9291 Discontinuation Follow Up** **30 days after Discontinuation by telephone or site visit**	**For Details See Section**
Safety Monitoring (In accordance with national product label)	As Clinically Indicated	X	As Clinically Indicated	
AZD9291 dispensing (daily dosing) via IxRS	X[1]			7.2.1
Serious Adverse events	X[2]		X	6.4
Urine or serum pregnancy test (WOCBP only)	As Clinically Indicated			5.2.1.1

[1] Once every 28 day cycle, contact with IxRS (call or web) for drug dispensing can be performed up to a maximum of 2 days prior to patient visit

[2] Ongoing monitoring and reporting of SAEs

Table 2 Group B: Study Plan detailing the procedures for the AZD9291+ MEDI4736 combination arm or MEDI4736 Monotherapy

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**																		**Treatment Discontinuation**	**For Details See Section**
		C1		**C2**		**C3**		**C4**		**C5**		**C6**		**C7**		**C8-C12**		**C13+**			
Day	**-28**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**		
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28-46**	**28-46**	**48+**	**50+**		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16-25**		**26+**	**27+**		
Window	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**0**	
Written informed consent/assignment of patient identification number[3]	X																				3.3 & 4.1
Assessment of T790M mutation status from recent biopsy[4]	X																				4.1 & 5.6.1.1
Archival tumour tissue sample[12, 5]	X																				5.6.1.2
Optional Tumour tissue for exploratory biomarker assessments[6]																				X	5.6.1.3
Optional genetic consent & sampling		X																			5.5.1& 5.5.2

[3] Consent may be taken prior to the 28-day window, if required. The screening period will start with first study-related assessment, excluding the biopsy collection of the tumour tissue sample for central T790M mutation

[4] Taken following progression on the most recent line of treatment. An FFPE tumour tissue sample (block or 10-20 sections) for T790M and PD-L1 testing should be provided. The same tumour tissue samples will be used for T790M and PD-L1 testing however PD-L1 testing will be done retrospectively

[5] Archival tumour sample only to be submitted after T790M positive status confirmed by central testing. Not required for T790M negative patients

[6] Optional FFPE biopsy at the time of progressive disease will be obtained for patients with accessible tumours where patients' consent has been obtained

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**																		**Treatment Discontinuation**	**For Details See Section**
		C1		**C2**		**C3**		**C4**		**C5**		**C6**		**C7**		**C8-C12**		**C13+**			
Day	**-28**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**		
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28-46**	**28-46**	**48+**	**50+**		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16-25**		**26+**	**27+**		
Window	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**0**	
Formal verification of eligibility criteria	X	X																			3.1 & 3.2
Medical and surgical history	X																				4.1 & 5.3.1
Demography and history of tobacco and alcohol use	X																				5.3.1
Previous treatments for NSCLC	X																				5.3.1
ECHO/MUGA	X	At least every 16 weeks (+/- 1 week) relative to first dose																			5.2.2.7
Ophthalmologic examination	X	As clinically indicated																			5.2.2.8
Hepatitis B and C and HIV	X																				5.2.2.1
Thyroid function test[7]	X	X		X		X		X		X		X		X		X		X		X	5.2.2.1
Coagulation parameters	X	As clinically indicated																			5.2.2.1
Urine or serum pregnancy test (WOCBP only)	X	As clinically indicated																			5.2.2.1

[7] TSH testing for all patients. Free T3 and T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system.

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**																		**Treatment Discontinuation**	**For Details See Section**
		C1		**C2**		**C3**		**C4**		**C5**		**C6**		**C7**		**C8-C12**		**C13+**			
Day	**-28**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**		
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28-46**	**28-46**	**48+**	**50+**		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16-25**		**26+**	**27+**		
Window	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**0**	
Clinical chemistry (including liver enzyme panel) / Haematology / Urinalysis	X	X[8]	X	X		X		X		X		X		X		X		X		X	5.2.2.1
Pharmacokinetic assessment for AZD9291 and MEDI4736		X			X			X						X				X Cycle 13 only			5.4.1
Immunogenicity assessment (ADA sampling - including ADA neutralizing antibodies)		X						X						X						X	5.4.3
sPD-L1 concentration (serum)		X						X						X							5.4.2
ctDNA plasma collection	X	X		X		X				X				X		Cycle 9 & 11 Only		X Cycle 13 only		X	5.6.2
Physical examination	X	X		X		X		X		X		X		X		X		X		X	5.2.2.3
WHO performance status	X	X		X		X		X		X		X		X		X		X		X	5.2.2.3

[8] If screening laboratory assessments are performed within 14 days prior to Cycle 1 Day 1 (first dosing day), they do not need to be repeated at Day 1.

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.)	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**																		**Treatment Discontinuation**	**For Details See Section**
		C1		**C2**		**C3**		**C4**		**C5**		**C6**		**C7**		**C8-C12**		**C13+**			
Day	**-28**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**		
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28-46**	**28-46**	**48+**	**50+**		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16-25**		**26+**	**27+**		
Window	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**0**	
Vital signs (pre- during and post-infusion vital signs assessments)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.2.5
Weight	X	X		X		X		X		X		X		X		X		X		X	5.2.2.6
Height	X																				5.2.2.5
ECG (locally assessed)	X	X		X		X		X		X		X		X		X		X		X	5.2.2.4
AZD9291 dispensing (daily dosing)[9]		X		X		X		X		X		X		X		X		X			7.2.1
MEDI4736 Infusion[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		7.2.2
Adverse events	All Visits																			X	6.3 & 6.4
Concomitant medications	All Visits																			X	3.6 & Appendix E
Tumour assessment (RECIST v1.1) [10]	X	every 8 weeks (+/- 7 days) relative to first dose for the first 48 weeks then every 12 weeks (+/- 7 days) thereafter until confirmed progression (according to modified RECIST 1.1)																			5.1.1 & 5.1.2

[9] Contact with IxRS (call or web) for drug dispensing can be performed up to a maximum of 2 days prior to patient visit

[10] If a patient has only one measureable lesion, it is acceptable to be used as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed. For all patients in this study, a confirmation of progression scan is required at no less than four weeks and preferably at the

Table 3 Study plan detailing the safety follow-up procedure for Group B patients of patients who have discontinued MEDI4736 for patients receiving AZD9291 + MEDI4736 combination therapy or MEDI4736 Monotherapy

Evaluation	Time since last dose of MEDI4736 Day (±3)			For details see Section
	30	60	90	
Physical examination	X			5.2.2.3
WHO performance status	X	X	X	5.2.2.3
Vital signs, including weight	X			5.2.2.5 & 5.2.2.6
ECG[11]	X			5.2.2.4
Clinical chemistry (including liver enzyme panel) / Haematology / Urinalysis	X	X	X	4.3.1 & 5.2.2.1
Thyroid function test[12]	X			5.2.2.1
Urine or serum pregnancy test (WOCBP only)	X			5.2.2.1
Immunogenicity assessment (ADA sampling – including ADA neutralizing antibodies)			X	5.4.3
MEDI4736 Pharmacokinetic assessment			X	5.4.1
Adverse events	X	X	X	6.3 & 6.4
Concomitant medications	X	X	X	3.6 & Appendix E

next scheduled visit after first overall visit response of PD. If progression is not confirmed then the patient should continue to have RECIST 1.1 assessments according to the study schedule until confirmed objective progression. Refer to Section 5.1.2 for further details.

[11] Only required if an on-treatment assessment was abnormal at the time of treatment discontinuation, to confirm reversibility of the abnormality

[12] TSH testing for all patients. Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system.

Evaluation	Time since last dose of MEDI4736 Day (±3)			For details see Section
	30	60	90	
Anti-cancer treatment	X	X	X	4.3
Tumor assessment (CT or MRI) (RECIST 1.1) [13]	every 8 weeks (+/- 7 days) relative to first dose for the first 48 weeks then every 12 weeks (+/- 7 days) until confirmed progression (according to modified RECIST 1.1) [14]			5.1.1 & 5.1.2

[13] Only applicable if a patient discontinues MEDI4736 for reasons other than confirmed disease progression

[14] Assessment not required after 90 days from last dose of MEDI4736

4.1 Enrolment/screening period

It is recommended the screening assessments be performed in a stepwise process beginning with the confirmation of T790M mutation status as determined by the designated central laboratory. However, screening assessments may be done in parallel to the T790M mutation assessment, as appropriate. Procedures will be performed according to the Study Plan (Table 1 and Table 2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study, provided the assessments fall within the protocol specified period prior to randomization.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be randomized into the study.

Patients will be considered in screening/enrolment period until all Visit 1 assessments are completed and eligibility is confirmed. Patients will be considered randomized and in the treatment period once study treatment has been initiated.

Written informed consent/Assignment of patient enrolment/randomization number:

- Each potential patient will provide written informed consent prior to starting any study specific procedures (see Section 10.4).
- All patients will be required to provide consent to supply a tumour biopsy sample for entry into this study. This consent is included in the main patient informed consent form. Please note that patients are asked to provide separate consent for provision of an optional discontinuation tumour biopsy sample, if willing (see Section 5.6.1.3).
- As per standard, the enrolment number (E-code) is assigned to a patient and the Principal Investigator or delegate should perform a screening/enrolment call (see Section 3.3). During the randomization visit, a patient will receive randomization number and randomized treatment arm information via IVRS/IWRS.

Mandatory screening tumour biopsy sample for prospective T790M and retrospective PD-L1 analysis:
Tumour tissue sample must be formalin fixed and paraffin embedded (FFPE) and must be biopsied following progression on the latest line of therapy and be less than 3 months old, except if technically not feasible and after discussion with the study physician. For those patients who do not have a recently acquired sample and where the collection of new biopsies is clinically feasible it is recommended that 2 core samples will be obtained and placed in formalin and processed as described in the Laboratory Manual.

Samples may be collected from primary or metastatic tumour deposits. Bone samples (including soft tissue tumoural masses emerging from the bone) cannot be accepted for testing. Sites should ship the FFPE tumour tissue sample to the testing laboratory as soon as it is available. Blocks must be provided wherever possible. If this is not possible, the following should be submitted:

- **For T790M & PD-L1 testing -** a minimum of 10-20 slides of freshly prepared unstained 5-micron sections (mounted on positively charged slides) from the mandatory screening FFPE tumour block may be provided. Tissue sections should be less than 60 days old from date of sectioning to date of testing.

The mandatory screening tumour biopsy must not be taken from a previously irradiated lesion or the lesion(s) selected for Inclusion criterion # 8. This biopsy sampling is not subject to the 28-day screening window. If tissue is already available from a biopsy taken since documentation of disease progression on the most recent treatment regimen and is <3 months old then there is no need for a further biopsy as this sample can be submitted for analysis. If the first biopsy is not confirmed as T790M mutation positive due to test failure (i.e., an invalid result), testing can be repeated and an additional biopsy sample may be requested. A sample with a valid mutation test result cannot be re-tested. A rescreened patient can provide tissue from a new biopsy sample for mutation testing, if required.

4.2 Treatment period

A cycle of treatment is defined as 28 days of once daily AZD9291 oral treatment (monotherapy arm), 28 days of once daily AZD9291 treatment in combination with MEDI4736 IV every 2 weeks (combination arm).

Group A - AZD9291 Monotherapy arm: Patients receiving AZD9291 monotherapy patients will follow the study plan according to Table 1

Group B - AZD9291+MEDI4736 Combination arm: Patient will follow the schedule of assessments column of Table 2. Visits will be every 2 weeks while patient is receiving MEDI4736 (for IV infusion requirements). If a patient stops MEDI4736 due to toxicity or Investigator judgement but continues dosing with AZD9291, the patient can begin to follow the Group A assessment scheduled (Table 1) after the required 90 day follow up assessment period has been completed (See Section 4.3). Patients may also discontinue AZD9291 and continue on MEDI4736 monotherapy, however these patients will not be permitted to restart AZD9291 and switch to the Group A assessment schedule at a later time.

There is no maximum duration of treatment as patients may continue to receive AZD9291 alone or MEDI4736 alone or in combination (AZD9291+MEDI4736) beyond RECIST 1.1 defined progression as long as they are continuing to show clinical benefit, as judged by the Investigator.

4.3 Follow-up period

Patients receiving AZD9291 monotherapy, should be contacted 30 days after their last dose of AZD9291 to follow up regarding any existing SAEs and monitor for new SAEs that may be related to IP. See Table 1.

After discontinuation of MEDI4736, patients who were randomized and received AZD9291 + MEDI4736 combination therapy should complete their 90 day follow up regardless of whether AZ9291 is continued as a monotherapy (See Table 3).

If a patient continues to receive AZD9291 monotherapy after MEDI4736 discontinuation, the follow up procedure outlined below applies:

- Patients that discontinue AZD9291 <60 days from discontinuing MEDI4736, will complete the 90 day follow up schedule from last date of MEDI4736 administration according to Table 3
- Patients that discontinue AZD9291 60-90 days after stopping MEDI4736 will complete the 90 day follow up as per Table 3 and also complete the safety follow up as per Table 1 up to 30 days post discontinuation of AZD9291
- Patients that discontinue AZD9291 >90 days after stopping MEDI4736 4736 will complete the 30 day safety following discontinuation of AZD9291 as per Table 1

4.3.1 Discontinuation visit

At the time study treatment is permanently discontinued, patients in Group A who were receiving AZD9291 monotherapy will not have a scheduled discontinuation visit but will be monitored in accordance with standard clinical practice or national product label. Refer to Table 1.

For patients who were randomized to receive AZD9291 + MEDI4736 combination therapy and MEDI4736 is permanently discontinued, a discontinuation visit will be performed according to Table 2.

4.4 Patient management following last patient's discontinuation of MEDI4736

When the final patient discontinues MEDI4736 and completes the required follow up period, the clinical study database will close to new data. Patients are, however, permitted to continue to receive AZD9291 beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment. Dispensing of study treatment post final MEDI4736 discontinuation will be done outside of IWRS. Patients who remain on study treatment after this time point will be monitored according to routine clinical practice as defined by the Investigator. At routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed at the site.

For patients who do continue to receive treatment beyond the final patient discontinuing MEDI4736, investigators will continue to report all SAEs, overdoses and pregnancies to AstraZeneca via paper and emailed (preferably) or faxed directly to TCS (also known as AZ

DES) in accordance with Section 6.4, 6.5 and 6.6. If an investigator learns of any SAEs, including death, at any time after a patient from either Group A or Group B has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the IP, the investigator should notify AstraZeneca (see Section 6.4). Additionally, as stated in Section 6.3, any SAE or non-serious AE that is ongoing at the time of the study database closure, 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.

5. STUDY ASSESSMENTS

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

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

Tumour assessments in GROUP A are not required. Tumour assessment will be performed in accordance with clinical practice and scans will no longer be collected.

5.1.1 RECIST 1.1

All imaging assessments, including unscheduled visit scans, should be maintained locally for the duration of the study. Scans should be available for review by AstraZeneca upon request.

RECIST 1.1 criteria will be used to assess each patient's tumour response to treatment and allow calculation of PFS, ORR, DCR, DoR, PFS landmark, and assess tumour shrinkage. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria [CR (complete response), PR (partial response), SD (stable disease) or PD (progression of disease)] are presented in Appendix C. See Section 5.1.1 for considerations related to RECIST 1.1 assessment time points.

The methods used at baseline (screening) for assessment of tumour burden [CT or MRI scans of chest and abdomen (including liver and adrenal glands)] must be used at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of an individual patient. CT/MRI scan of the

brain should be performed in patients with known or suspected brain metastases with the same frequency as for CT/MRI chest and abdomen assessments. The baseline assessment should be performed within 28 days of treatment start. Assessments to be performed every 8 weeks relative to first dose for the first 48 weeks and every 12 weeks thereafter until confirmed objective disease progression. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ± 7day window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Any other sites at which new disease is suspected should also be appropriately imaged.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesions (NTLs) 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 substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

For patients who discontinue study treatment due to toxicity in the absence of confirmed objective progression, tumour assessments should be continued every 8 weeks for 48 weeks (relative to the date of first dose/infusion) and then every 12 weeks until confirmed objective disease progression up to a maximum of 3 months after the last dose of MEDI4736. Patients on monotherapy AZD9291 will be assessed according to local practice until objective disease progression.

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

5.1.2 RECIST Modification for Confirmation of Progression

RECIST 1.1 has been modified to take into consideration the unique response kinetics which has been observed with immunotherapy in some patients where responses to immune therapies may occur after progression (PD) assessed (Wolchok et al 2009). To ensure an unbiased assessment, patients in both arms of the study should be treated and followed up post initial progression until subsequent disease progression (confirmed progression).

For patients in Group B, a confirmation of progression scan is required at no less than four weeks and preferably at the next scheduled visit after first overall visit response of PD. Confirmed progression is defined as:

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

If progression is not confirmed then the overall visit response should be assessed as SD/PR or CR and the patient should continue scheduled RECIST 1.1 CT/MRI scans until confirmed objective disease progression by modified RECIST 1.1 or up till 3 months after discontinuation of MEDI4736, whichever occurs first. The initial RECIST 1.1 assessment of progression should not be updated if not confirmed at subsequent assessments unless it was equivocal with respect to non-target or new lesions. If progression is confirmed the overall visit response should be assessed as PD.

5.2 Safety assessments

5.2.1 Safety assessments of Patients on AZD9291 Monotherapy

5.2.1.1 Laboratory safety assessments

Laboratory safety assessments should be performed as per national product label for patients in Group A receiving AZD9291 monotherapy.

5.2.1.2 Physical examination

Physical examinations should be performed as per national product label for patients in Group A receiving AZD9291 monotherapy.

5.2.1.3 Resting 12-lead ECG

Patients in Group A receiving monotherapy AZD9291 will be assessed or national product label.

5.2.1.4 Vital signs

Vitals should be assessed as per national product label for patients in Group A receiving AZD9291 monotherapy.

5.2.1.5 Weight

Weight will be checked at the Screening Visit and then per national product label for the duration of the study for patients in Group A receiving AZD9291 monotherapy.

5.2.1.6 Echocardiogram/MUGA scan

LVEF should be assessed as per national product label for patients in Group A receiving AZD9291 monotherapy.

5.2.1.7 Ophthalmic Examination

Ophthalmic examination should be performed as per national product label for patients in Group A receiving AZD9291 monotherapy.

5.2.2 Safety assessments of Patients on MEDI4736 in combination with AZD9291 or on MEDI4736 monotherapy

5.2.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan tables (see Section 4).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 4 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin	S/P-Albumin
B-Haematocrit	S/P-Alkaline phosphatise (ALP)
B-Leukocyte count	S/P-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)	S/P-Aspartate transaminase (AST)
Neutrophils	S/P-Bilirubin, total
Lymphocytes	S/P-Calcium, total
Monocytes	S/P-Creatinine
Basophils	S/P- Glucose
Eosinophils	S/P-Magnesium
B-Platelet count	S/P-Phosphate
B-Red blood cell (RBC) count	S/P-Potassium
B-Reticulocytes	S/P-Sodium
	S/P-TSH[1]
Urinalysis	S/P- Urea or blood urea nitrogen (depending on local practice)
U-Blood	
U-Glucose	
U-Protein	

Blood (B), Serum (S), Plasma (P), Urine (U)
[1] Free T3 and Free T4 to be measured only if TSH is abnormal. Also to be measured if there is clinical suspicion of an adverse event related to the endocrine system.

Additionally, at the Screening Visit, the following assessments will be performed:

- Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be collected for women of childbearing potential only
- Lactate dehydrogenase (LDH)
- Hepatitis B surface antigen, hepatitis C antibody, HIV antibody
- Coagulation parameters: Activated partial thromboplastin time (PTT) and International normalised ratio (INR) to be assessed at Screening and as clinically indicated

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

5.2.2.2 Volume of Blood

Total mandatory blood volume in first 16 weeks is 107 mL (monotherapy arm) and 152 mL (combination arm).

Table 5 Blood sample volumes (in mL/per patient)

Visit	Safety (both arms)	AZD9291 PK Analysis (mono arm)	AZD9291+ MEDI4736 PK Analysis (combo arm)	ctDNA Plasma (both arms)	sPD-L1 conc & ADA/nAb (combo arm)	PGx (both arms)
Screening	15	0	0	20	0	10 (optional)
Cycle 1	10	6	16.5	10	12	0
Cycle 2	10	6	16.5	10	0	0
Cycle 3	10	0	0	10	12	0
TOTAL (mandatory)	**45**	**12**	**33**	**50**	**24**	**0**

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific changes.

5.2.2.3 Physical examination

A physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems. Height will also be captured at the screening visit only.

World Health Organization (WHO) Performance Status:

Performance status will be assessed at the visits indicated in the Study Plan (see Table 2 & Table 3) according to WHO criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions
1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

5.2.2.4 Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the patient has been resting supine or semi-supine for at least 10 minutes prior to times indicated and should be recorded at 25 mm/sec. All ECGs should be recorded with the patient in the same physical position. An ECG machine following the local standard should be used and the patient should be examined using the same machine throughout the study, where feasible.

All ECG data will be assessed and maintained locally and will be captured in the eCRF, including at a minimum: HR, PR, RR, QRS, QT and overall evaluation.

ECGs will be performed at the visits indicated in the Study Plan (see Table 2 & Table 3)

For Group B AZD9291+MEDI4736 combination arm:

- Screening Visit
- Cycle 1 Day 1:
  - Pre-dose (within 1 hour prior to infusion of MEDI4736),
  - Within 30 minutes post end of infusion
- From Cycle 2 onward for all treatment cycles: Pre-dose ECG only
- Treatment Discontinuation
- 30-days after last dose of MEDI4736 - if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality
- On occurrence of any cardiac AE

After ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. If there is a clinically significant abnormal ECG finding during the Treatment period, this should be recorded on the AE eCRF, according to standard adverse events collection and reporting processes. Results should be stored locally and will no longer be stored or assessed centrally.

Heart rate, PR, R-R, QRS and QT intervals should be assessed.

5.2.2.5 Vital signs

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

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Body temperature is only required at Screening and when clinically indicated.

On infusion days, patients in the AZD9291+MEDI4736 combination arm will be monitored during and after infusion of MEDI4736 as presented in the bulleted list below. Patients in the AZD9291 monotherapy arm will be monitored pre-dose only and as clinically indicated.

Blood Pressure and pulse will be collected from patients in the AZD9291+MEDI4736 combination arm before, during, and after the infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)
- A 1-hour observation period is recommended after the first infusion of MEDI4736. If no infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each MEDI4736 infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs and management of abnormalities seen is at the discretion of the Investigator per standard clinical practice, national product label (if approved) or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.6.

5.2.2.6 Weight

Weight should be checked at the Screening Visit, Day 1 of each cycle and at the Treatment Discontinuation Visit for the AZD9291+MEDI4736 combination arm. Additional assessments can be made as per local practice.

5.2.2.7 Echocardiogram/MUGA scan

An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to first dose of AZD9291 or MEDI4736), then at least every 16 weeks (+/- 1 week) from the time of first dose throughout the treatment period, when clinically indicated and followed up regularly to resolution if an abnormal reading is measured.

The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible. Quantitative LVEF results, not estimates, must be provided.

5.2.2.8 Ophthalmic Examination

Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results should be collected in the eCRF.

Ophthalmic assessment will be performed at Screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests, if clinically indicated.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for central review by AZ and AZ representatives if necessary. Ophthalmology examination results should be collected in the eCRF.

Patients experiencing corneal ulceration will not be permitted to restart study treatment.

5.3 Other assessments

5.3.1 Baseline Characteristics

Baseline demographics, ethnicity, smoking history, alcohol consumption, disease history, previous treatments and EGFR mutation information and race and/or ethnicity according to local regulations will be collected.

5.4 Pharmacokinetics

In protocol version 2.0, collection of pharmacokinetics samples for patients following the GROUP A study plan are no longer required.

5.4.1 Collection of pharmacokinetic samples

Venous blood samples for determination of concentrations of MEDI4736 and AZD9291 including metabolites (AZ7550 and AZ5104) will be taken at the times presented in Table 6.The date and time of collection of each PK sample and the date and time of dose (on PK day and day prior) will be recorded.

Table 6 PK blood sample schedule for the AZD9291 + MEDI4736 combination arm

Time relative to dose	Cycle 1 Day 1 [1]	Cycle 2 Day 15	Cycle 4 Day 1	Cycle 7 Day 1	Cycle 13 Day 1	90 Days After Discontinuation
Pre-dose for AZD9291 (-10 to 0 mins)[2]	X	X	X	X	X	
Pre-dose for MEDI4736 (-10 to 0 mins)[2]	X					X
End of infusion (+5 mins)	X	X	X	X	X	
2 - 4 hours		X	X	X	X	

[1] AZD9291 will be administered first; the MEDI4736 infusion will start approximately 1 hour (maximum 2 hours) after AZD9291 administration. If there are no issues with the first cycle then for all other cycles the MEDI4736 can be given immediately after AZD9291 administration has finished. If dosing of MEDI4736 does not happen immediately following AZD9291 in Cycle 2 or onward PK collection times should be as noted in Cycle 1 Day 1 column. There is no 2-4 hr collection time point for Cycle 1 Day 1 as this is the same as the End of infusion time point due to study drug dosing requirements for this visit.

[2] Window of -10 minutes recommended where feasible (but up to -30 minutes permitted if assessments are performed in different locations in hospital).

If patients on the AZD9291+MEDI4736 combination arm stop either treatment, PK samples are only required for the determination of concentrations the patient is currently taking (ie., for patients only taking MEDI4736, PK samples for AZD9291 are not required).

The timing of the pharmacokinetic samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration time profiles. The total number of samples and the total volume of blood taken from each patient will not exceed that detailed in Section 5.2.2.2. Residual samples may be analysed for exploratory biomarkers.

If a patient misses any doses of AZD9291 or MEDI4736 within 7 days of PK sampling, please contact AstraZeneca to discuss any changes required on the timing of the PK assessments. All other assessments, including local laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to first dose.

Samples that have been collected will be labelled, stored and shipped as detailed in the Laboratory Manual.

5.4.2 Collection of soluble PD-L1 concentration samples

Blood (serum) samples will be collected for analysis of circulating soluble factors in relation to immune status at baseline and in response to treatment. Samples for soluble PD-L1 concentration are obtained from patients in the AZD9291+MEDI4736 combination arm only as per Table 2 and Table 3 while patients are taking MEDI4736. If MEDI4736 is stopped due to toxicity or progression, further soluble PD-L1 sampling is not required**.**

5.4.3 Collection of samples to measure for the presence of ADAs (Immunogenicity)

The presence of ADA (including ADA neutralizing antibodies) will be assessed in serum samples taken pre-dose (prior to MEDI4736 infusion) at the visits indicated in the Study Plan tables (see Table 2 and Table 3). These samples will be collected from patients only in the combination AZD9291+MEDI4736 arm of the study while patients are taking MEDI4736. If MEDI4736 is stopped due to toxicity or progression, further immunogenicity sampling is not required.

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive-negative cut points previously statistically determined from drug-naïve validation samples will be employed.

5.4.4 Determination of drug concentration

Samples for determination of MEDI4736 and AZD9291 (including metabolites) concentrations in plasma will be analysed by a designated third party on behalf of AstraZeneca using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest, at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the pharmacokinetic samples may be subjected to further analyses by AstraZeneca in order to further investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

5.4.5 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

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

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AZ Biobank; see details in the Laboratory Manual).

5.5 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study a blood sample will be collected.

AstraZeneca intends to perform genetic research in the AZD9291 and MEDI4736 clinical development programmes to explore how genetic variations may affect the clinical parameters associated with AZD9291 alone or in combination with MEDI4736.

The benefits of being able to explore associations between genes and clinical outcomes within the AZD9291 and/or MEDI4736 programmes are potentially many and include:

- analysis of genes that may affect efficacy, safety and tolerability (for example, but not limited to, drug metabolising enzymes and drug transporters)

- genetic research into genes that may contribute to the risk of NSCLC (for example, but not limited to, mutations in the gene encoding EGFR)

The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report.

5.5.1 Collection of pharmacogenetic samples

The patient's consent to participate in the pharmacogenetic research components of the study is optional.

The single blood sample (10 mL) for genetic research will be obtained from the patients prior to the first administration of AZD9291 or MEDI4736 in the study. If for any reason the sample is not drawn prior to dosing it may be taken at any visit until 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. Such patients would be important to include in any genetic analysis. Only one sample should be collected per patient for genetics during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.5.2 Storage, re-use and destruction of 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 Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

Refer to Appendix F for details of the optional DNA genetic research.

5.6 Exploratory biomarker analysis

Biological samples (e.g., plasma, archived and study-obtained tumour, etc) may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes.

The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies.

5.6.1 Collection of tumour biopsy samples

5.6.1.1 Mandatory screening tumour tissue sample for central T790M testing and retrospective PD-L1 expression analysis

Mandatory tumour tissue samples provided for central T790M testing will be used to retrospectively assess PD-L1 expression as part of biomarker research. Access to the tumour tissue block is preferred as uncontrolled oxidation processes affect tumour sections. Please refer to details of the sample requirements in Section 4.1.

5.6.1.2 Archival tumour sample

Formalin fixed archival tumour tissue embedded in paraffin blocks are to be retrieved for all patients, if available. The archival samples are preferably from the time of diagnosis and from

the primary tumour and/or metastatic site. Any biopsy samples taken following previous lines of therapy will also be requested, if available. In each case the previous patient treatment must be clearly indicated for each sample provided. Tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, 10-20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided. As uncontrolled oxidation processes affect tumour sections, tumour tissue blocks are preferred. From submitted archival tumour blocks, material may be taken for exploratory biomarker analysis (including 2 cores in order to construct tissue micro arrays) for later biomarker analysis. The remaining part of the tumour block can be returned to the institution.

This sample will be used to support exploratory biomarker analyses (see Section 5.6.3.1).

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

5.6.1.3 Optional tissue collection at progression

Formalin fixed paraffin embedded (FFPE) biopsies at the time of progressive disease will be obtained for Group B patients with accessible tumours where patients' consent has been obtained.

On-treatment biopsy timing may be refined with emerging pharmacokinetic and/or pharmacodynamic data during the course of the study. Accessible lesions are defined as tumour lesions, which are biopsiable, and amenable to repeat biopsy, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation. Where feasible, collection of a tumour biopsy at relapse is encouraged. This sample will be used to investigate changes in pathway signalling and potential mechanisms of resistance (ie, genetic alterations, evidence of alternative pathway activation).

For timings of all tumour biopsy samples requested see Table 7 below.

Table 7 Tumour biopsy samples

Time relative to dose	Requirement
Archival	M*
Screening	M[1]
Progression[2]	O

1 Refer to Section 4.1 for full details
2 To be taken at discontinuation or progression, whichever occurs first
M = Mandatory O = Optional M* = mandatory if available

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

5.6.2 Collection of plasma samples for circulating tumour DNA

All patients eligible for the study will be required to provide a series of plasma samples for ctDNA. All samples from randomization onward are to be drawn pre-dose as described in the Study Plan (Table 2) and below. These samples will be collected to provide plasma for circulating tumour DNA, for the analysis of predictive biomarkers and to interrogate changes in genetic alterations and potential mechanisms of resistance. Plasma samples collected on the study may also be used (in an exploratory fashion) to assess baseline characteristics and pharmacodynamic measures of drug activity. Patients in Group A are no longer required to provide plasma samples for ctDNA.

Table 8 Plasma for exploratory analyses

Visit (sample taken pre dose)	ctDNA collection
Screening	X
Cycle 1 Day 1	X
Cycle 2 Day 1	X
Cycle 3 Day 1	X
Cycle 5 Day 1	X
Cycle 7 Day 1	X
Cycle 9 Day 1	X
Cycle 11 Day 1	X
Cycle 13 Day 1	X
Treatment Discontinuation [1]	X
Time of Progression[2]	X

[1] Discontinuation samples should be taken upon discontinuation of the last study treatment. If drugs are stopped at different times, sample should be taken on discontinuation of the last investigational product.
[2] For patients who discontinue treatment prior to progression. This is only applicable for Group B patients who progress during the required follow up period (See Section 4.3).

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

5.6.3 Exploratory Analyses

5.6.3.1 Exploratory Biomarker Analyses

Biological samples (e.g., plasma, serum, archived and study-obtained tumour, etc) will be collected and may be analysed for exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to AZD9291.

The biomarkers to be investigated using tumour samples collected will not necessarily be limited to but will include all or some of the following:

- EGFR T790M mutation
- EGFR sensitising mutations (L858R, Exon 19 del, etc)
- p-EGFR
- PD- L1

5.7 Management of Biological Samples

5.7.1 Storage, re-use and destruction of biological samples

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. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological 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 B '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 and appropriate labelling, shipment and containment provisions are approved.

All tumour samples should be shipped at ambient temperature as per the Laboratory Manual to the AstraZeneca designated central Contract Research Organisation.

5.7.3 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.

AstraZeneca 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 during the entire life cycle.

5.7.4 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 is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- 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 of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca 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.

AstraZeneca ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical

studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., 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 A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from the time of signature of informed consent throughout the study until the completion of the follow up period. The follow-up period is defined as 30 days +/- 3 days after study treatment is discontinued in the AZD9291 monotherapy arm, and is 90 days (3 months) +/- 7 days after study treatment is discontinued in the AZD9291+MEDI4736 combination arm. (See section 4.3)

SAEs will be recorded from the time of informed consent. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4).

After the completion of the follow up period, no additional other information will be collected for this trial. When the final patient discontinues MEDI4736, there may be some patients receiving treatment with AZD9291 (either from those randomised to receive AZD9291 or randomised to receive AZD9291 +MEDI4736 but who have discontinued MEDI4736). For these patients who are continuing to receive AZD9291, AstraZeneca will collect information (during the treatment period until the end of the follow up period) on SAEs, overdose and pregnancy via paper and emailed (preferably) or faxed directly to TCS (also known as AZ DES). Drug accountability information will be recorded in the patient notes. See Section 4.4.

6.3.2 Follow-up of unresolved adverse events

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 CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product(s)
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- 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 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

The grading scales found in the current National Cancer Institute (NCI) CTCAE version will be utilised for all events with an assigned CTCAE grading. For those events without assigned

CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

6.3.5 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 CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated safety parameters 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.

If deterioration in a laboratory value, vital sign, ECG, or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., 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).

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.

6.3.7 Hy's Law

Cases where a patient shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The Investigator is responsible for, without delay, determining whether a patient meets potential Hy's law (PHL) criteria.

Details of identification of PHL cases and actions to take are detailed in Appendix D.

6.3.8 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.

6.3.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

6.3.10 Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes

6.4 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 CRF.

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

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

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

If an Investigator learns of any SAEs, including death, at any time and he/she considers there is a reasonable possibility that the event is related to study treatment, the Investigator should notify AstraZeneca. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

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

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

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

6.5 Overdose

There are no data on overdosing since this is one of the first studies with AZD9291 administered in combination with MEDI4736 in humans. There is no definition of what constitutes an overdose. There is no known antidote to either of these agents.

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.

- An overdose with no associated symptoms is only reported on the overdose CRF module.

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

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

For overdoses associated with a SAE, standard reporting timelines apply, see Section 6.4. For other overdoses, reporting should be done within 30 days.

6.6 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca using the appropriate forms during the course of the study and the 30 day follow up period (see Section 6.6.2 for more details).

6.6.1 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 adverse event 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 or within 30 days of the final dose of the investigational product, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately **but no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing ends should be followed up and documented.

6.7 Management of IP related toxicities and individual stopping criteria

If a patient experiences a clinically significant and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, dosing will be interrupted or the dose reduced and supportive therapy administered as required.

Please note: Recommendations for appropriate management of clinically significant and/or intolerable AEs considered by the Investigator to be causally related to AZD9291 or MEDI4736, are located in Section 6.7.1 and Appendix G.

All dose interruptions or reductions will be recorded in the appropriate electronic system ie, eCRF.

6.7.1 Toxicity management and dose modifications to AZD9291

All patients to commence treatment at the starting dose level as shown in Table 9.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with the study drug dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, study drug may be restarted at the same dose (starting dose) or reduced dose 40 mg AZD9291 at the Investigator discretion and with discussion and agreement with Study Physician if needed.

If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient will be permanently withdrawn from the study treatment after discussion with the study medical monitor/physician and observed until resolution of the toxicity. There will be no individual

modifications to treatment schedule in response to toxicity, only potential dose reduction or dose interruption.

Patients with Grade 3 QTcF prolongation (i.e. confirmed QTcF to > 500 msec absolute or a > 60 msec increase from baseline) should have study treatment interrupted and regular ECGs performed until resolution to baseline. If the QTcF interval resolves to Grade 1 (<481 msec), study drug may be restarted at the reduced dose of 40 mg AZD9291 at the Investigator discretion and with discussion and agreement with Study Physician if needed. If the QT prolongation does not resolve to ≤CTCAE grade 1 (<481 msec) after 3 weeks, then the patient will be permanently withdrawn from study treatment after discussion with the Study Physician and observed until resolution of the toxicity.

Table 9 AZD9291 dose modifications

Dose at time of toxicity	Reduced dose level
80 mg OD (starting dose)	40 mg OD
40 mg OD	No further reduction possible

Dose re-escalation will not be permitted in this study.

On resolution of toxicity within 3 weeks:
If an AE subsequently requires dose interruption, AZD9291 may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be sent to Investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued. In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the AstraZeneca Study Team Physician

Patients with QTcF prolongation to >500 msec on at least 2 separate ECGs must have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline QTcF is ≥481 msec; and then restarted at a reduced dose of 40mg. If there are signs/symptoms of serious arrhythmia, or if the toxicity does not resolve to grade ≤1 (i.e. QTcF <481 msec), or to baseline QTcF, within 21 days, the patient will be permanently discontinued from study treatment.

Patients experiencing any of the following will not be permitted to restart study treatment:

- Corneal ulceration
- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

Recommendations for appropriate management of skin reactions, including guidance on dose-adjustments for clinically significant and/or intolerable skin reactions that are considered by the investigator to be causally related to AZD9291 will be provided to investigators.

Recommendations for appropriate management of diarrhoea, including dose-adjustments for adverse events of diarrhoea that are of CTCAE grade ≥3 or that are clinically significant and/or intolerable and considered by the investigator to be causally related to AZD9291, will be provided to investigators.

Discussions may be required with AstraZeneca as to any effect on the PK sample schedule if the interruption occurs within 3 days of PK sampling. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per Table 2 & Table 3.

6.7.1.1 Management of Immune-related Adverse Events

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and MDX-1106 including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Hodi et al 2010; Brahmer et al 2010). Patients should be monitored for signs and symptoms of irAEs. In absence of alternate etiology (eg, infection or PD) signs or symptom of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune related. It is recommended that management of irAEs follow the guidelines outlined for ipilimumab (Weber et al 2012; Yervoy™ package insert 2011). The management guidelines are summarised in Table 10.

Table 10 Management of Immune-related Adverse Events

1	Patient evaluation to identify any alternative etiology
2	In the absence of a clear alternative etiology, all events of inflammatory nature should be considered to be immune related
3	Symptomatic and topical therapy should be considered for low-grade events
4	Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
5	More potent immunosuppressives should be considered for events not responding to systemic steroids

6.8 Study governance and oversight

6.8.1 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) was established to review safety and supportive efficacy assessments and make recommendations to continue, amend, or stop the study based on findings. The IDMC planned to initially meet when approximately 70 patients had been randomized and followed up for 3 months (estimated to be 6 months from first patient randomized). However due to the results of the TATTON trial showing an increased incidence of Interstitial Lung Disease (ILD) in a subset of patients similar to CAURAL, recruitment was terminated early in this trial and the pre-defined number of enrolled patients required for IDMC review was not achieved. The IDMC supported this decision. In light of the early termination of recruitment, limited number of patients dosed in the study and the change in study scope, the IDMC, coordinating investigators and AstraZeneca have agreed that there is no further scope for IDMC to monitor the study.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength
AZD9291	40-80 mg Tablets
MEDI4736	10 mg/kg solution, IV

7.2 Dose and treatment regimens

This study consists of 2 treatment arms (randomized on a 1:1 ratio):

1. **Monotherapy arm:** AZD9291 80 mg, orally, once daily

compared to

2. **Combination arm:** AZD9291 (80 mg, orally, once daily) in combination with MEDI4736 (10 mg/kg (IV) infusion every 2 weeks.

NOTE: For the combination arm only – AZD9291 will be administered first; the MEDI4736 infusion will start approximately 1 hour (maximum 2 hours) after AZD9291 administration. If there are no issues with the first cycle then for all other cycles the MEDI4736 can be given immediately after AZD9291 administration has finished.

7.2.1 AZD9291

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 80 mg.

At each dispensing visit, sufficient AZD9291 for 28 days treatment, plus overage, will be dispensed. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Patients should swallow one AZD9291 80 mg tablets once daily, commencing on Cycle 1 Day 1. Tablets should be taken whole with water.

The dose of AZD9291 can be reduced under circumstances described in Section 6.7

On clinic days on which PK samples are scheduled to be taken, the dosing should be delayed until arrival at the clinic and until the pre-dose ECG has been performed followed by the pre-dose PK sample. Patients should not take their dose until instructed to do so by site personnel.

Doses should be taken approximately 24 hours apart at the same timepoint each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their AZD9291, they should not make up for this dose, but should take the next scheduled dose.

Any change from dosing schedule, dose interruptions and dose reductions should be recorded in the eCRF. Drug accountability information for Group A (AZD9291 Monotherapy) will be stored in the patient notes at the site.

Tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Bottles will be dispensed to patients in the AstraZeneca packing provided. The packaging includes bottles, caps and a label. Bottle tampers should not be broken prior to dispensing study drug to a patient.

Additional information about the Investigational product may be found in the Investigators' Brochure.

7.2.2 MEDI4736

MEDI4736 will be supplied by AstraZeneca as a 500-mg vial concentrate for solution for infusion. The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. Total in-use storage time from needle puncture of MEDI4736 vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the in-use storage time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded.

Preparation of MEDI4736 doses for administration with an IV bag

Dose of 10 mg/kg will be administered using a 250-mL IV bag containing 0.9% (weight/volume) saline and delivered through an IV administration set with a 0.2-µm in-line filter.

Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. A volume of 0.9% (weight/volume) saline equal to the calculated volume of 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 MEDI4736 (in mL) to add to the IV bag is calculated as follows:

In combination with AZD9291: 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 a 250 mL 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.

Additional information about the Investigational product may be found in the IB.

Suggested guidelines for monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in Section 5.2.2.5.

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 patient. 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.

7.3 Labelling

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

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the pack/bottle/carton specifies the appropriate storage. Storage is also described in the IB.

7.5 Compliance

The administration of all study drugs should be recorded in the appropriate sections of the Case Report Form.

Patient should return all unused medication and empty containers to the Investigator.

7.6 Accountability

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

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

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed.

7.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening (4 weeks prior to starting study treatment) until the end of the safety follow

up phase of the study (as shown in Table 3). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. Guidance on medications that require close monitoring is given in Section 3.6 and Appendix E.

Restricted, prohibited, and permitted concomitant medications are described in the following tables.

Prohibited medication/class of drug:	**Usage:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given while the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given while the patient is on study treatment through 90 days after the last dose of IP.
Any concurrent chemotherapy, local therapy (except palliative radiotherapy for non-target lesions, eg, radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given while the patient is on study treatment. Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and TNF-α blockers	Should not be given while the patient is on study treatment. Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Live attenuated vaccines	Should not be given through 30 days after the last dose of study treatment during the study

Rescue/supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management, etc)	Should be used when necessary for all patients
Blood transfusions	Allowed at any time during the study.
Bisphosphonates	Patients may receive treatment with bisphosphonates for the treatment of bone metastases.

Palliative radiation	Patients may receive radiotherapy for painful bony metastases.

7.7.1 Other concomitant treatment

Medications other than those described in Section 3.6 and Appendix E that are considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator and should be recorded in the appropriate sections of the eCRF.

7.8 Post study access to study treatment

Patients receiving AZD9291 alone at the time of study completion may continue to receive if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment. Patients who remain on study treatment after this time point will be monitored according to routine clinical practice as defined by the Investigator. At routine clinic visits, patients will return used and unused medication, and a thorough drug accountability assessment will be performed at the site.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

To investigate the safety and tolerability profile of AZD9291 in combination with MEDI4736.

Although a comprehensive Statistical Analysis Plan (SAP) was prepared and finalised prior to first subject in (FSI), the SAP will be updated accordingly after the approval protocol version 2.0.

There will be two main summaries of the data presented overall. Safety and tolerability related summaries will comprise of patients who received at least one dose of randomised treatment, where efficacy summaries will use all patients randomised on the study, regardless of the treatment actually received.

A primary summary will be performed with a data cut-off date representative of when last country with active patients receives ethics and regulatory approval for protocol version 2.0. Patients will be summarised according to the randomised treatment. All statistical analyses for PFS have been replaced with descriptive summary of the number of events and percentage (where appropriate).

A final addendum summary will be performed when the last patient discontinues MEDI4736 and completes their required safety follow up. Only data collected between the primary summary data cut-off and the time when last patient receiving MEDI4736 reaches the end of safety follow up, will be summarised. Patients will be summarised by Group A (patients

receiving AZD9291 monotherapy either due to randomisation or due to discontinuing MEDI4736) and group B (patients receiving MEDI4736 either as combination or as monotherapy).

If all patients have discontinued from MEDI4736 treatment at the time of DCO for the primary study summary, the primary summary will become the only summary of data for the study.

In all instances of summaries, due to the small study population caused by early study termination it is not appropriate to perform statistical testing between groups.

Multiple Testing Strategy

The safety, tolerability and efficacy of the AZD9291+MEDI4736 combination and AZD9291 alone will be reported descriptively with no hypothesis testing being performed between treatment arms. As a result, no adjustment for multiple testing is required.

8.2 Sample size estimate

Under the original study design, PFS was the primary endpoint, and approximate 350 patients were to be randomized for the formal statistical evaluation of the treatment difference in the primary efficacy endpoint.

As the safety issue was identified from the combination treatment of AZD9291 and MEDI4736 in TATTON study, recruitment was terminated earlier than planned. At the time of stopping the recruitment, 60 patients had been screened and 29 patients had been randomized by the pre-specified stratum factors of the number of previous lines of treatment (2nd or 3rd+) and ethnicity (Asian or Non-Asian).

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients. The full analysis set will be used for all efficacy summaries, and treatment groups will be compared on the basis of randomized treatment, regardless of the treatment actually received.

8.3.2 Safety analysis set

The safety analysis set will consist of all patients who received at least one dose of randomized treatment. Safety data will be summarised using the safety analysis set, according to the treatment that patients received in their first cycle. Additional summaries might be provided for the patients who were randomised and received the combination but later discontinued MEDI4736 as appropriate.

8.3.3 PK analysis set

Patients in the FAS who have at least one measurable PK concentration, supported by the relevant date and time of this sample and for each time a PK sample was taken the dosing data for that day and for samples taken after multiple dosing the dosing data for the 2 days prior to the sample day as well as the sample day. For any individual sample to be included in the PK analysis set the full sample data and dosing data needs to be present for that sample.

8.4 Outcome measures for analyses

Patients receiving AZD9291 monotherapy will have no clinical data collected, other than serious adverse events, outcomes of pregnancy, drug dispensing/accountability and overdose. Patients continuing to receive AZD9291 will contribute to the summary the data which had been previously recorded on study.

8.4.1 Calculation or derivation of efficacy variables

Investigator RECIST based assessments

From the Investigators review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. It will also be used to determine the endpoints ORR, DoR, DCR and PFS from the overall visit response and scan dates.

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

Please refer to Appendix C for the definitions of Complete Response, Partial Response, Stable Disease and Progressive Disease.

Progression Free Survival (PFS) Landmark Summary

PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression. Patients who remain alive and progression free at the timepoint for the landmark assessment will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

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

RECIST 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

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

The progression-free survival landmark summaries will be reported as the proportion of patients alive and progression free at 6 and 12 months (per RECIST1.1 as assessed by the investigator). Kaplan Meir estimates for progression-free survival will be reported.

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Objective Response Rate (ORR)
ORR rate is defined as the number (%) of patients with measurable disease with at least one visit response of CR or PR that is confirmed at least 4 weeks later. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation.

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

Duration of Response (DoR)
Duration of response will be defined as the time from the date of first documented response, (that is subsequently confirmed) until 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 PFS endpoint. 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. If the response is not confirmed, it will not be included.

If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

Disease control rate (DCR)
Disease control rate is defined as the percentage of patients who have a best overall response of CR or PR or SD.

Tumour shrinkage
Tumour shrinkage will be assessed using RECIST tumour response. The absolute change and percentage change from baseline in sum of tumour size at each assessment will be calculated. The best change in tumour size will include all assessments prior to progression or start of subsequent anticancer therapy.

Overall Survival (OS) Landmark Summary

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 the summary 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 2 weeks following the date of the data cut-off and if patients are confirmed to be alive, or if the death date is post the data cut-off date, these patients will be censored at the date of the data cut off. Death dates may be found by checking publicly available death registries.

Overall survival landmark summary will be reported as the proportion of patients alive at 12 months. Kaplan Meier plots and estimates will be produced at the time of summary.

8.4.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP), ECG and WHO performance status. These will be collected for all patients prior to this version of the protocol.

Adverse events

AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient.

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

Any AE occurring within 90 days of discontinuation of investigational product (ie, the last dose of AZD9291/MEDI4736) will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of AZD9291/MEDI4736) will be flagged in the data listings. Please refer to Section 6.3.1

Other significant adverse events (OAEs)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's 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 (pulse and BP)/ECG data/ ECHO/MUGA/WHO status will be performed for identification of OAEs.

Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

8.4.3 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic summary of the plasma concentration data for MEDI4736, AZD9291 and AZ5104 and AZ7550 will be performed by a designated third party or delegate on behalf of AstraZeneca. Plasma concentration will be summarized by normal time window. The ratio of metabolite (AZ5104 or AZ7550) to AZD9291 will be calculated.

The plasma concentration data for AZD9291 and metabolites and/or MEDI4736 will also be analysed using a population pharmacokinetic approach, which may include exploring the influence of covariates on PK, if the data allows. A pharmacodynamic (PD) or pharmacokinetic-pharmacodynamic (PK-PD) approach may be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate.

The data collected in this study may also be combined with similar data from other studies and explored using population pharmacokinetic and/or pharmacokinetic-pharmacodynamic method. The results of any such analyses will be reported separately from the Clinical Study Report.

8.5 Methods for statistical analyses

Safety and tolerability related summaries will comprise of patients who received at least one dose of randomised treatment, where efficacy summaries will use all patients randomised on the study, regardless of the treatment actually received.

In all instances of summaries, due to the small study population caused by early study termination it is not appropriate to perform statistical testing between groups. As a result there will be no hypothesis testing performed and all summaries will be reported descriptively instead..

8.5.1 Summary of the primary variable

There will be two main summaries of the data presented overall, unless there will be no patients continuing to receive MEDI4736 treatment after the DCO for the primary study summary in which case only primary summary will be performed.

A primary summary will be performed with a data cut-off date representative of when last country with active patients receives ethics and regulatory approval for protocol version 2.0. Patients will be summarised according to the randomised treatment. The safety and tolerability of AZD9291 plus MEDI4736 combination and AZD9291 monotherapy treatment arms will be summarised by reporting adverse events, laboratory data, vital signs (pulse and BP), ECG and WHO performance status.

All adverse events, both in terms of MedDRA PT and CTCAE grade, will be listed and summarized descriptively by count (n) and percentage (%) for each treatment group. Additional summary tables will be provided to report serious adverse events, AE of special interest, and adverse events considered causally related to the study drugs by the investigator.

The remaining safety and tolerability data will also be summarised descriptively for the absolute values and the change from baseline.
A final addendum summary will be performed when the last patient discontinues MEDI4736 and completes their required safety follow up. Only data collected between the primary summary data cut-off and the time when last patient receiving MEDI4736 reaches the end of safety follow up, will be summarised. Available safety data will be summarised and the number of events and percentage will be shown for: all Group A patients, Group A patients who were randomised to AZD9291 monotherapy and Group A patients who were initially randomised to AZD9291 + MEDI4736 treatment, and all group B patients.

8.5.2 Summary of the exploratory variable(s)

8.5.2.1 Landmark Summary of PFS

Progression status assessed by investigator at time of landmark analyses (at Month 6 and Month 12 from the last subject first dose) will be summarised.

Kaplan Meier plots and estimates will be produced at time of landmark summary along with other descriptive summaries based on the FAS.

8.5.2.2 Landmark Summary of OS

The proportion of patients alive at 12 months will be reported. Kaplan Meier plots and estimates will be produced at the time of summary

8.5.2.3 Summary of ORR

ORR will be analyzed in terms of the proportion of responders out of the number of available patients per treatment arm. The associated 95% confidence intervals will also be provided using the Clopper-Pearson exact method for binomial proportions.

8.5.2.4 Summary of DoR

DoR will be reported using summary statistics to describe the duration of response in those patients with an initial response on study.

8.5.2.5 Summary of DCR

DCR will be presented as the proportion of patients with disease control, out of the number of patients available per treatment arm. The associated 95% confidence intervals will also be provided using the Clopper-Pearson exact method for binomial proportions. .

8.5.2.6 Summary of Tumour Shrinkage

The best absolute change in target lesion tumour size from baseline and percentage change in target lesion tumour size from baseline will be summarized using descriptive statistics and presented at each time point and by randomized treatment group. .

8.5.2.7 Pharmacokinetics

Pharmacokinetic concentration data and the ratio of metabolite to AZD9291 will be listed and summarised using appropriate summary statistics and further details will be provided in the SAP.

8.5.2.8 Remaining exploratory outcomes

Deoxyribonucleic acid (DNA) collected for exploratory research into genes or genetic variation and tumour and blood-based (plasma and serum) samples collected for exploratory research into factors that may influence susceptibility to development of NSCLC/cancer may also be analysed retrospectively. Further details of summaries and analyses for any exploratory objectives maybe documented in a separate analysis plan as required and may be reported outside the CSR in a separate report

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

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 CRFs, 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 CRFs 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 (e.g., clinic charts)

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

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

9.1.1 Source data

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

9.1.2 Study agreements

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

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

9.1.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.2 Study timetable and end of study

The end of the study is defined as when last patient receiving MEDI4736 (either as monotherapy or in combination with AZD9291) has permanently discontinued MEDI4736 and has completed their 90 day safety follow up (section 4.3)

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 AZD9291 or MEDI4736.

9.3 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff, according to the Data Management Plan. 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. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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

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

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

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

Serious Adverse Event (SAE) Reconciliation
SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data
Any genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

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

AstraZeneca 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**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician 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.

10.2 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

AstraZeneca 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**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician 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.

10.3 Ethics and regulatory review

An Ethics Committee 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.

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

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions 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.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigators 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 10.3.

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.

10.6 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, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Additional Safety Information

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

Life threatening

'Life-threatening' means that the 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.

- 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 hospitalization
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the 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?

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

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

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

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

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

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

- Is there a known mechanism?

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

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

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

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

Labelling and shipment of biohazard samples

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

1. Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1) guidelines (Eisenhauer et al 2009) for the 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 at least one measurable lesion at baseline that can be accurately assessed by computerised tomography (CT), magnetic resonance imaging (MRI) or plain X-ray should be included in this study.

Measurable lesions:

- At least one lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short access ≥ 15mm) with CT or MRI which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used as long as it has not been previously irradiated and the baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

Non-measurable lesions:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)

- 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 are not measurable by CT or MRI

- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment

- Lesions chosen for biopsy during the study screening period if still present should be selected as NTL at baseline and follow up as part of the NTL assessment **unless** they fulfil the criteria for measurability when there is only one measurable lesion existing.

- Skin lesions assessed by clinical examination

- 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 non-cystic lesions should be selected as the 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 TLs should be identified as NTLs at baseline.

3. Method of Assessment

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

The methods to be used for RECIST assessment are summarised in Table 11 and those excluded from tumour assessments in this study are discussed below, with the rationale provided.

Table 11 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

3.1 CT and MRI

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

In this 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

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI or plain Xray and to identify the presence of new lesions.

3.3 X-rays

3.3.1 Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

3.3.2 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

3.4 Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs 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

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

3.6 Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment 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 the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs 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 NTLs and followed by the same method as per baseline assessment.

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

FDG-PET (18-Fluoro-deoxyglucose positron emission tomography) 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 FDG uptake (defined as when an uptake greater than twice

that of the surrounding tissue is observed) 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.

4. Tumour response evaluation

4.1 Schedule of evaluation

CT examinations of the chest and abdomen (including liver adrenal glands) will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contract media administration is the preferred method. MRI should be used where CT is no feasible or it is medically contra-indicated.

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. CT/MRI scan of the brain should be performed in patients with known or suspected brain metastases with the same frequency as for CT/MRI chest and abdomen assessments. Follow-up assessments to be performed every 8 weeks (± 7 days) relative to the first dose for the first 48 weeks and then every 12 weeks (± 7 days) thereafter until confirmed objective disease progression (as defined by RECIST 1.1 modified for confirmation of progression in this study) or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs 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 TLs will be calculated and reported

as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs 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 > 5mm, 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 5mm.
- 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 etc, during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

Table 12 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 12 Overall Visit Response for 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 TLs, taking as reference the baseline sum of diameters.

Table 12 Overall Visit Response for Target Lesions

Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive 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 5mm.
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
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.

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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. Table 13 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 13 Overall Visit Response for 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 NTLs.

Table 13 Overall Visit Response for Non-Target Lesions

Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

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 SD or PR 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 study treatment without objective evidence of disease progression at that time should continue to undergo RECIST 1.1 assessments according to the clinical study protocol 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 14

Table 14 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Target lesions	Non-Target lesions	New Lesions	Overall response

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs at baseline)

5. RECIST Modification for Confirmation of Progression

RECIST 1.1 has been modified to take into consideration the unique response kinetics which has been observed with immunotherapy in some patients where responses to immune therapies may occur after progression (PD) assessed (Wolchok et al 2009). To ensure an unbiased primary endpoint, patients in both arms of the study should be treated and followed up post initial progression until subsequent disease progression (confirmed progression).

For all patients in this study, a confirmation of progression scan is required at no less than four weeks and preferably at the next scheduled visit after first overall visit response of PD. Confirmed progression is defined as:

- ≥20 % increase in sum diameters of target lesions compared to the nadir at 2 consecutive visits (with an absolute increase of at least 5mm)

- and/or significant progression (worsening) of NTLs or New Lesions (NL) at the confirmatory PD time-point compared with the first time point where progression of NTLs or NLs identified

  and/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first time point NLs identified

If progression is not confirmed then the overall visit response should be assessed as SD/PR or CR and the patient should continue scheduled RECIST 1.1 CT/MRI scans until confirmed objective disease progression my modified RECIST 1.1. The initial RECIST 1.1 assessment of progression should not be updated if not confirmed at subsequent assessments unless it was equivocal with respect to non-target or new lesions. If progression is confirmed the overall visit response should be assessed as PD.

6. Confirmation of Response

In this study, imaging for confirmation of response (CR or PR) should be performed at the next scheduled RECIST assessment

7. 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.

8. 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. of Cancer 2009; 228-247.

Wolchok et al 2009
Wolchok JD, Hoos A, Bohnsack O, Weber JS, O'Day S, Hamid O, et.al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria, Clin Cancer Res 2009;15(23): 7412-20

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

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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)

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

Hy's Law (HL)

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

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. 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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. Follow-up

4.1 Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- 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 (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- 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. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
- 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 << with liver metastases>> who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

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

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in 4.2 Potential Hy's Law Criteria met of this Appendix

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

7. Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, << or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment >>?

If No: follow the process described in 4.2 Potential Hy's Law Criteria met 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 the section 4.2 of this Appendix

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

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

Appendix E Guidance regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

1. DRUGS INDUCING CYP3A4 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH AZD9291

AZD9291 is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of AZD9291 evaluated in patients showed that there is potential for AZD9291 being a victim when co-administered with strong inducers of CYP3A4 (AZD9291 concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving AZD9291.

Table 15 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to AZD9291 start
Avasimibe, Carbamazepine, mitotane, phenobarbital, phenytoin Rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Enzalutamide, Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

2. MEDICINES WHOSE EXPOSURES MAY BE AFFECTED BY AZD9291 THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

AZD9291 may increase the concentrations of sensitive BCRP substrate (concentrations of sensitive BCRP substrate, rosuvastatin is increased).

Table 16 Exposure, pharmacological action and toxicity may be increased or decreased by AZD9291

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD9291.

3. DRUGS THAT MAY PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by, Tucson, Arizona and Rockville, Maryland.

3.1 Drugs known to prolong QT interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland.

Table 17 Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to AZD9291 start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks

Table 17 Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to AZD9291 start
Amiodarone, chloroquine	1 year

*Estimated value as pharmacokinetics of arsenic trioxide has not been studied

3.2 Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 18 Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to AZD9291 start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8weeks

Appendix F Pharmacogenetics Research

1. Background and Rationale

AstraZeneca intends to perform genetic research in the AZD9291 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9291 alone and in combination with MEDI4736. Collection of deoxyribonucleic acid (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 AZD9291 or MEDI4736 but also susceptibility to the 'response'/disease for which AZD9291 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

2. Genetic Research Objectives

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD9291 alone and in combination with MEDI4736.

3. Genetic Research Plan and Procedures

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol, Section 3.1.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main body of the Clinical Study Protocol, Section 3.2.

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 3.7 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 1 or after randomisation. 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), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 5.2.2.2 of the Clinical Study Protocol.

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 subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is 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.

4. Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the 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 centre. 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. 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. Also Regulatory authorities may 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 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.

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.

Appendix G MEDI4736 Toxicity Management Guidelines

Toxicity management and dose modifications to MEDI4736

Toxicity management for Immune-mediated adverse events related to MEDI4736 are presented in Table 19. Toxicity management for Infusion Related Reactions related to MEDI4736 are presented in Table 20 and Toxicity management for Non-immune Mediated Reactions reactions are presented in Table 21.

No dose reductions are permitted with MEDI4736, only dose delays or permanent withdrawal of MEDI4736.

The below tables provide details of Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for MEDI4736 Monotherapy. The grading scale utilised is the NCI CTCAE V4.03.

Table 19 Immune-Mediated Reactions

	Dose Modifications	Toxicity Management
Immune-related Adverse Events (Overall Management For toxicities not noted below)	Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	It is recommended that management of irAEs follow the guidelines presented in this table – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) – In the absence of a clear alternative etiology, all events should be considered potentially immune related. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events – For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone 1-2mg/kg/day PO or IV equivalent – 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 PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (> 28 days of taper) – More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – 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
	Grade 1 No dose modification Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study treatment can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper – Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as	

Table 19 Immune-Mediated Reactions

	Dose Modifications	Toxicity Management
	per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	
	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)	General Guidance	– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose 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) – 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 – Consider pulmonary and infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 – If toxicity worsens then treat as Grade 3 or Grade 4 If toxicity improves to ≤ Grade 1 then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper	– For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – 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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[15] – Consider pulmonary and infectious disease consult – Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen	– For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consult – Hospitalize the patient – Supportive Care (oxygen, etc.) – 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 – 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)[i]
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	General Guidance	– 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,

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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			peritoneal signs and ileus) - 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.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	- For Grade 1 diarrhea : - Close monitoring for worsening symptoms - 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 - If toxicity worsens then treat as Grade 3 or Grade 4 - If toxicity improves to ≤ Grade 1, then study drug/study regimen can be resumed after completion	- For Grade 2 diarrhea: - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide - Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent - 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. - If still no improvement within 3-5 days despite 2-4mg/kg IV

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		of steroid taper	methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[16]). . **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult study physician if no resolution to ≤ Grade 1 in 3-4 days – 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])

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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen	– For Grade 3 or 4 diarrhea: – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging and/or colonoscopy as appropriate – 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). – Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – 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])
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of**	Grade of Liver Function Test Elevation (CTCAE version 4.03) Any Grade		– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Immune Related Hepatitis	Grade 1 (AST or ALT > to 3 times ULN and/or TB > to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	– For Grade 1 AST or ALT and/or TB elevation – - Continue LFT monitoring per protocol
	Grade 2 (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 – If toxicity worsens then treat as Grade 3 or Grade 4 – If improves to baseline ≤ Grade 1 or baseline, resume study drug/study regimen after completion of steroid taper	– For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[17] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**.

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

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– 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 (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 – Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline – Resume study drug/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days, and after completion of steroid taper – Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days – For elevations in transaminases	– For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – 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.** – Hepatology consult, abdominal workup, and imaging as appropriate. – 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 of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		> 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen - Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[ii]	
	Grade 4 (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) Any Grade	General Guidance	- Consult with Nephrologist - Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) - Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event

	Grade 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: – Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 – 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 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper	– For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. – 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]). – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	- Carefully monitor serum creatinine on daily basis - Consult Nephrologist and consider renal biopsy if clinically indicated - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - 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 (Please refer to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	- Monitor for signs and symptoms of dermatitis (rash and pruritus) - **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	- For Grade 1: - Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper	– For Grade 2 : – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is 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 PO or IV equivalent – 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 – 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: – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once 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]) – Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)	General Guidance	– Consult Endocrinologist – 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. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. – 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 (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) – Monitor patient with appropriate endocrine function tests – 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.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2 (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 - If toxicity worsens then treat as Grade 3 or Grade 4 - Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper - Patients with endocrinopathies who may require prolonged or continued steroid replacement 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) - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Initiate hormone replacement as needed for management - Evaluate endocrine function, and as clinically indicated, consider pituitary scan - 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). - - 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]) - For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (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 - Resume study drug/study regimen administration if controlled at the next scheduled dose - 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: - Consult endocrinologist - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - Administer hormone replacement therapy as necessary. - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity - Once improving, gradually taper immunosuppressive 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]) - Discuss with study physician
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-	Grade of Neurotoxicity Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for		

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Barre)	defining the CTC grade/severity		
	Any Grade	General Guidance	– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – 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 • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. o If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study regimen can be resumed once event	– Discuss with the study physician – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG) –

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		improves to Grade ≤1 and after completion of steroid taper	
	Grade 3	• Hold Study drug/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	– For Grade 3 or 4: – Discuss with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) – Once stable, gradually taper steroids over ≥28 days
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		General Guidance	– 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 – 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 – 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

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			be best facilitated by means of a neurology consultation - 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 not responsive to IVIG
	Grade 1	No dose modification	- Discuss with the study physician - Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above - Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	- Hold study drug/study regimen dose until resolution to ≤ Grade 1 - Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	- Grade 2 - Discuss with the study physician - Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above - Obtain a Neurology Consult - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) - *MYASTHENIA GRAVIS* 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. 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.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			○ 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. – *GUILLAIN-BARRE:* ○ 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 3	– Hold study drug/study regimen dose until resolution to ≤ Grade 1 – 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: – Discuss with study physician – Recommend hospitalization – Monitor symptoms and obtain neurological consult – *MYASTHENIA GRAVIS* ○ Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. ○ 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. – *GUILLAIN-BARRE*: – 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
	Grade 4	Permanently discontinue study drug/study regimen	

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			plasmapheresis if not responsive to IVIG

Table 20 Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	- Management per institutional standard at the discretion of investigator - Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, 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	For Grade 1 or Grade 2: - Acetaminophen and/or antihistamines may be administered per

Table 20	**Infusion-Related Reactions**	
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	resolution of the event	institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses – Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Table 21	**Non-immune Mediated Reactions**	
Severity Grade of the Event (NCI CTCAE version 4.03)	**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

Table 21	**Non-immune Mediated Reactions**	
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modification**	**Toxicity Management**
		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 For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
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

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