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**Clinical Study Protocol**

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| Drug Substance | Durvalumab (MEDI4736)<br>and tremelimumab |
| Study Code     | D419AC00003                               |
| Version        | 9.0                                       |
| Date           | 20 Jan 2020                               |

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

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**Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden**

**EudraCT Number: 2015-002197-21**

## VERSION HISTORY

### **Version 9, 12 Dec 2019**

Changes to the protocol are summarized below.

#### **Section 1.3.2 Overall risks**

- Updates per Durvalumab IB edition 14 section 1.3.2.1 & 1.3.2.3
- Updates per Tremelimumab IB edition 9 section 1.3.2.2

#### **Post Data Cut Off (DCO) section in Protocol Synopsis & section 7.2.2**

Post Data cut off options were updated to clarify the treatment options post final analysis

#### **Section 6.5 Adverse Events of Special Interest**

Updated the AEs of Special interest as per AESI list from Durvalumab IB edition 14

#### **Section 6.10: Management of IP-related toxicities**

Section 6.10 was newly added to align with the requirement of managing the Toxicity management guidelines as an Annexure to the protocol. Section 6.10.1 & 6.10.2 were also updated

#### **Appendix E Management of investigational product-related toxicities**

Appendix E which included the Toxicity management guidelines was removed as link provided in Section 6.10 replaces Appendix E.

#### **Section 7.1.1 and 7.1.2**

Addition of density to sections 7.1.1 & 7.1.2

#### **Section 7.8: Post study access to study treatment**

Section updated to clarify options related to continuation of study treatment post the Final analysis of patients in global cohort and China cohort.

### **Version 8, 03 April 2019**

Changes to the protocol are summarized below.

#### **International Coordinating Investigator**

Update PPD to PPD

#### **Protocol Synopsis, Section 1.1.5 Rationale for conducting this study, Section 1.2.4 Rationale for endpoints, Section 2.1 Primary Objectives, Section 2.2 Secondary Objectives,**

Based on the evolving understanding of immune checkpoint inhibitor therapy there was a need for amendment to the original objectives proposed in this study. The primary objective was changed from PD-L1  $\geq 25\%$  to bTMB  $\geq 20\text{mut}/\text{Mb}$ . Multiple bTMB cutoffs, PD-L1  $< 1\%$  and tTMB cutoffs were added as additional secondary endpoints.

#### **List of Abbreviations and definition of terms:**

Updated the list to include new terms such as IC, INR, APTT, TMB, bTMB and tTMB.

#### **Protocol Synopsis, Section 1.1.1 Immunotherapies**

Updated to include the rationale for changing primary endpoint to bTMB  $\geq 20\text{mut}/\text{Mb}$ .

#### **Protocol Synopsis, Section 1.4 Study Design**

Updated to add definition of bTMB high.

#### **Section 1.1.2 MEDI4736**

Updated the total number of patients (6000) dosed with MEDI4736 as a part of ongoing studies to reflect the latest data based on the updated CSP template.

#### **Section 2.4 Exploratory objectives**

The 3 additional exploratory objectives were added with the intention to explore potential biomarkers in residual biological samples (e.g. tumor and blood) including but not limited to, somatic mutations and gene expression in tumor and blood samples, which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to derive increased benefit to durvalumab + tremelimumab combination therapy.

#### **Section 5.5 Biomarker analysis, 8.5.12 Biomarker data**

Updated to include details of bTMB and tTMB testing and analysis.

#### **Section 6.5 Adverse Events of Special Interest**

Updated to include AE's (vasculitis, non-infectious meningitis and non-infectious encephalitis) as per the revised AE SI list

#### **Section 6.1.9, Post Data Cut Off (DCO) sections of Protocol Synopsis and Section 7.2.2**

Updated text to clarify the data collection options for long term overall survival after Final analysis

**Section 6.9 Medication Error, Appendix A(A1)**

Updated to include Medication error reporting process as per new CSP template requirement.

**Section 8.1 Statistical considerations, Section 8.6 China Cohort**

Updated to include the China specific considerations in China specific SAP.

**Section 8.2 Sample size estimate**

This has been re-estimated in alignment to the revised objectives.

**Section 8.3 Definitions of analysis sets**

Updated the analysis sets according to revised objectives.

**Section 8.5 Methods for statistical analysis**

Updated the statistical and sensitivity analysis including update to multiple testing procedures for controlling the type I error rate.

**Section 9.3 Study timetable and end of study**

Updated the study end date as per the latest predictions

**Section 11 List of REFERENCES**

Updated to include 13 new references.

**Version 7, 02 February 2018**

Changes to the protocol are summarized below.

**Synopsis, Section 6.1.9 Safety Data to be Collected Following the Final DCO of the Protocol Study, Section 7.2.2 Duration of treatment and criteria for treatment through progression and for retreatment**

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

**Protocol Synopsis, Section 8.2 Sample size estimate, Section 8.5 Methods for statistical analysis, Section 8.5.13 Interim analysis, Section 8.6 China cohort**

In order to ensure sufficient follow-up for both efficacy and safety prior to conducting the analysis, the protocol has been updated to outline that only a final analysis of OS will be conducted. The interim analysis, planned to occur after approximately 80% of the target

events has been removed. In addition, the maturity of the final analysis has been increased. The statistical analysis sections have been updated accordingly.

### **Section 1.3.2 Potential Risks**

Since the NEPTUNE study commenced, the MEDI4736 programme has developed and the emerging safety profile has become more established. As such, the “Potential Risks” section of this clinical study protocol has been updated to align and be consistent with the broader MEDI4736 programme, including the Investigator Brochure

**Section 4, Study plan and timing of procedures, Table 2 and Table 3, Section 5.4.3, Storage and destruction of pharmacokinetic/ADA samples, Section 5.5.1 Collection of patient samples for stratification by PD-L1, Section 5.5.3 Tumour samples collected in China for PD-L1 testing will be destroyed or repatriated maximally 5 years after study drug is approved for marketing in China, Section 5.5.5 Chain of custody of biological samples, Section 5.5.6 Withdrawal of informed consent for donated biological samples**

These sections are updated based on China regulatory requirement on handling biological samples

### **Section 6.3.1, Time Period for Collection of Adverse Events**

Updated to clarify collection timeline for an event that starts post the defined safety follow up period.

### **6.3.2, Follow-up of unresolved adverse events**

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

### **6.4 Reporting of serious adverse events**

Clarity provided on handling safety events post final DCO

### **6.5 Adverse events of Special interest**

Updated based on latest IB

### **Section 8 Statistical Analysis**

Clarified text regarding SAP finalisation/amendment. Updated wording regarding analysis populations to be consistent with Table 9. Added further clarity on analysis by stratification factors and the handling of re-treatment data.

### **Section 11 List of References**

Updated to include 6 references.

### **Appendix E Management of investigational product-related toxicities**

Updated to align with the most current Investigator Brochure.

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

Updated to include the most current version of the Dosing Modification and Toxicity Management Guidelines.

### **Terminology update**

Updated terminology from immune-related Adverse Event (irAE) to immune-mediated Adverse Event (imAE). Duruvulamub wording has been updated to MEDI4736 keep it consistency across the CSP

### **Version 6, 18 September 2017**

Changes to the protocol are summarized below.

#### **Protocol Synopsis, Section 8.2 Sample size estimate, Section 8.5 Methods for statistical analysis, Section 8.5.13 Interim analysis, Section 8.6 China cohort**

In order to ensure there is sufficient follow-up for both efficacy and safety prior to conducting an interim analysis (IA), the protocol will retain only one IA after approximately 80% of the target death events have been observed. The first IA, currently planned after approximately 60% of the target events will be removed. The statistical analysis sections have been updated accordingly.

#### **Section 1.3.2.1 MEDI4736**

Updated with identified risks to include amylase and lipase increases and myocarditis. Additionally the percentage of patients that experienced an SAE that was considered to be related to monotherapy MEDI4736 by investigator was updated from 3.5% to 5%.

#### **Section 2.4 Exploratory Objectives, Section 5.5.1 Collection of patient samples for stratification by PD-L1, 5.5.2 Exploratory Biomarkers, Section 8.5.12 Biomarker data**

These sections were updated to clarify that OS, PFS, ORR, DoR and related outcome measures, e.g. OS12 will be assessed in subgroups defined by additional biomarkers e.g. tumor mutation burden and/or interferon-gamma signature assessed in tumor biopsies or gene expression in blood or circulating tumor DNA. These sections have been updated accordingly.

#### **Section 3.2 Inclusion criteria 12**

An estimated life expectancy of  $\geq 12$  weeks has been added. This is to ensure that patients enrolled into the study have a sufficiently long life expectancy such that they have the opportunity to gain benefit from study treatment and applicable to recruiting countries

#### **Section 3.2 Exclusion criteria 15**

Changed abbreviation of TB to full word for clarity.

#### **Section 5.3.1 WHO/ECOG performance status**

This was updated to include numbering and the insertion of criteria 5. Dead for both accuracy and clarity on performance status.

### **Section 6.5 Adverse Events of Special Interest**

Insertion of additional bullet with identified risk for Myocarditis.

### **Version 5, 02 February 2017**

Changes to the protocol are summarized below.

#### **Synopsis, Section 1.4 Study design, Section 2.0 Study objectives, Section 5.1.1 Central reading of scans and 8.2 Sample size estimate**

These sections are updated with addition of options to continue recruitment in mainland China, following achievement of the global recruitment target of 800 randomized patients and a. further objective to evaluate consistency in efficacy and safety among Chinese subjects as required by China health authority.

#### **Synopsis, Section 1.4 Study design, Section 2.0 Study objectives and 8.2 Sample size estimate**

Updated to reflect the design change to incorporate China cohort and co-primary endpoints on PD-L1-positive<sub>25%</sub> population and inclusion of additional analysis population PD-L1-positive<sub>1%</sub> and the relevant additional analysis required Synopsis,

#### **Synopsis, Glossary and Section 1.4**

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

#### **Synopsis, Section 7.2.2 Duration of treatment and criteria for treatment through progression and for retreatment**

Title and wordings in these sections were updated based on Durva project level CSP standard template to be consistent across program.

#### **Section 1.1 Background and rationale for conducting this study & 1.3 Benefit/risk and ethical assessment (subsections)**

These sections and subsections were updated based on updated information available.

#### **Section 3.2: Exclusion 9, 14, 15, 18 and 19**

Due to deletion of exclusion criteria 14, subsequent exclusion criteria numbers changed. The exclusion criterion 14 deleted as from current ongoing studies study drugs shown no impact on QTcF interval.

Exclusion criteria 9, 15 (previously 16), 18 (previously 19) and 19 (previously 20) have been clarified.

### **Section 3.3 Patient enrollment and randomization, Section 4.0 Study plan and timing of procedures, Section 5.6 Pharmacogenetics and Appendices**

In previous CSP version 4.0, genetic research option has been removed, as these are no more applicable. However, text related to genetic research in above mentioned sections along with Appendix C were inadvertently not removed. Hence, these sections have been updated by removing relevant texts in this version of the CSP.

Since, Appendix C is no longer applicable, subsequent appendices numbering have been updated.

### **Section 3.3 Patient enrollment and randomization and Section 4.1 Enrollment/screening period**

This section has been updated to clarify the relationship between informed consent and study specific procedure requirements.

### **Section 3.8 Restrictions, Table 1 Highly effective methods of contraception**

Hormonal contraception methods were clarified further.

### **Section 3.9.1 Procedures for discontinuation of a patient from investigational product**

This section updated to clarify the requirement of RECIST assessment post discontinuation of study drugs.

### **Section 3.10.2 Withdrawal of the informed consent**

This section has been updated to clarify that necessary questions are to be raised to the patient while patient decides to withdraw the consent.

### **Section 3.10.2.1 Survival status for withdrawn consent and lost to follow up patients**

This section has been updated to clarify the difference between lost to follow-up cases and withdrawal case.

### **Section 3.11 Discontinuation of the study**

Further clarified with reason for study discontinuation.



**Section 4.0 Study plan and timing of procedures, Table 2 Schedule of assessments for MEDI4736 + tremelimumab combination therapy treatment and retreatment periods and Table 3 Schedule of assessments for Standard of Care therapy treatment period**

This Section updated to further clarity on RECIST assessment requirement.

In previous CSP version 4.0, section 5.2.1 Laboratory safety assessment, table 7 were updated stating that ‘Urinalysis should be done at baseline (screening) and then as clinically indicated’. However, Table 2 schedule of assessment for urinalysis was not updated accordingly. Hence, this has been corrected in this CSP version.

Footnote of table 2 and table 3 updated on pregnancy test requirements.

**Section 4.1 Enrollment/screening period**

In this section timing of consent in relation to screening assessment are clarified.

**Section 4.3 Follow-up period**

This section has been updated to clarify the criteria for patient entering follow-up period.

**Section 5.1 Efficacy assessments**

This section was updated to provide clarity on efficacy assessments

**Section 5.2.1 Laboratory safety assessments**

Table 5 of this section was updated with an additional footnote giving abbreviations.

Table 6 was updated with additional Hematology tests (i.e., Basophils, Eosinophils) which should be routinely collected as part of the full blood count and are necessary to monitor safety based on the toxicity profile of the IP or SoC arms.

**Section 5.2.3 Electrocardiograms**

This section was updated by removing the requirement of calculating QTcF interval at screening (this is no longer applicable).

**Section 5.2.4 Vital signs**

Following paragraph has been removed as this procedure is no longer required.

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

**6.5 Adverse Events of Special Interest**

This section was added in order to be in line with program level standard requirement. Wordings are similar to Appendix E

### **Section 6.7 Pregnancy**

This section was updated by adding exception to pregnancy reporting.

### **Section 6.8 Management of investigational product-related toxicities**

This section was updated to be in line with program level standard requirement. Wordings are similar to Appendix E.

### **Section 7.1.1 MEDI4736 & 7.1.2 Tremelimumab**

These sections have been updated to provide further clarity on drug administration. Removed drug preparation information as it has been now referred to single document i.e., Drug Handling Instructions

### **Section 7.2.1 Treatment regimens**

This updated by providing clarity on MEDI and TREME infusion timings

### **Section 7.2.2 Duration of treatment and criteria for retreatment**

In this section, the statement below was inadvertently added and this has been removed (as fixed dosing is not applicable for this protocol.

‘During the retreatment period, patients in the durvalumab (MEDI4736) + tremelimumab combination therapy group will resume durvalumab (MEDI4736) dosing at 1500mg Q4W with 75 mg of tremelimumab Q4W for 4 doses/cycles each. Patients will then continue with durvalumab (MEDI4736) monotherapy at 1500mg Q4W, beginning at Week 16, 4 weeks after the last dose of combination therapy, until disease progression’.

### **Section 7.4 Storage**

Detailed clarity has been provided on storage requirement of study drugs.

### **Section 7.7 Concomitant and other treatments**

List of prohibited medications and its use have been updated based on treatment arm.

### **Section 7.7.2 MEDI4736 drug-drug interactions**

New section on drug-drug interaction information was added.

### **Section 8 Statistical Analysis by AstraZeneca**

Include a revised multiple testing strategy (as in figure 4)

Update relevant sections to reflect required changes to analysis based on inclusion of co-primary endpoint, the additional patient population of PD-L1-positive<sub>1%</sub> and the change to the multiple testing strategy

Includes a summary of the handling of the China cohort data (Section 8.6)

### **Section 10.5 Changes to the protocol and informed consent form**

Japan specific wordings updated.

### **Appendix A Additional Safety Information**

Drug-drug interaction wording removed as these are now added in CSP main section 7.7.2

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

This appendix with typo corrections added.

### **Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law**

This Appendix has been updated to clarify PHL reporting as per the new AZ CSP template.

### **Appendix D Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)**

Updated RECIST 1.1 guidelines have been incorporated which providing more clarity to Investigators during tumor evaluation. Additionally, typo corrections were completed.

### **Appendix E Management of investigational product-related toxicities**

This appendix was updated with the addition of new AEs of special interests.

### **Version 4, 04 October 2016**

Changes to the protocol are summarized below.

#### **Title pages**

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

## **Synopsis**

Patient follow-up post discontinuation of study drug was separately added to emphasize on the patient follow-up along with Survival.

### **Synopsis and Section 1.4 Study design**

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

Also clarified that crossover of SoC patient to MEDI4736 or MEDI4736 + tremelimumab combination therapy will not be permitted.

### **Synopsis, Section 1.3.1.3 MEDI4736 + tremelimumab combination therapy, Section 1.4 Study Design, Section 3.1 Inclusion criteria 6 and Section 8.3.2 PD-L1-negative population analysis set**

Updated CCI.

### **Synopsis, Section 1.4 Study design and Section 8.2 Sample size**

Total number of enrolled patients has been increased from 960 to 1330 by taking into consideration of the current screen failure rate.

### **Synopsis and Section 7.2.2 Duration of treatment and criteria for retreatment**

There remains a need to further investigate outcomes of patients on immunotherapy treatments who continue treatment until disease progression. Duration of treatment was therefore modified so that patients in the immunotherapy group can continue therapy until disease progression rather than stopping therapy at 12 months. This will allow patients who are benefitting from the immunotherapy treatment to continue on treatment and potentially reduce the risk of patients losing clinical benefit after treatment is discontinued at 12 months.

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

### **Synopsis and Section 2.2 Secondary Objectives**

Order of secondary objective changed to ensure PFS, ORR, DoR, and APF12 using Investigator assessments according to RECIST 1.1 comes before PFS, and ORR in patients with PD-L1–negative NSCLC.

**Section 1.1.1 Immunotherapies, 1.1.2 MEDI4736, 1.1.3 Tremelimumab, 1.1.4 MEDI4736 in combination with tremelimumab**

These sections are updated based on updated information available from ongoing studies.

**Section 1.2.1 MEDI4736 and tremelimumab dose and treatment regimen justification and subsections**

These sections are updated based on the updated information available from ongoing studies.

**Section 1.2.5 Rationale of retreatment option**

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

**Section 1.3 Benefit/risk and ethical assessment & subsections**

This section updated based on new safety information available in accordance with current Investigator Brochure.

**Section 3.1 Inclusion criteria 4 and 10**

Have been clarified.

**Section 3.2 Exclusion criteria**

Following Criteria were updated to provide clarity.

- Sarcomatoid variant of NSCLC is added as an exclusion criteria
- The part of the exclusion criteria of brain metastases or spinal cord compression and off steroids and anticonvulsants for at least 1 month prior to study treatment is amended to and off steroids for at least 14 days prior to study treatment. In addition, following radiotherapy and/or surgery, patients with brain metastases must wait 4 weeks after the intervention and must confirm stability with imaging before randomization
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or

Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

Patients with vitiligo or alopecia

Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

Any chronic skin condition that does not require systemic therapy

Patients without active disease in the last 5 years may be included but only after consultation with the study physician

Patients with celiac disease controlled by diet alone

- Supplementary information on the diagnoses are given:

HIV diagnosis requires positive HIV 1 or 2 antibodies

Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible

Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA)

- Any condition that, in the opinion of the Investigator, would interfere with the evaluation of IP or interpretation of patient safety or study results, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from MEDI4736 or tremelimumab, or SoC or compromise the ability of the patient to give written informed consent

Following criteria newly added.

- Prior randomization or treatment in a previous MEDI4736 and/or tremelimumab clinical study regardless of treatment arm assignment

### **Section 3.8 Restrictions**

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

- Male patients with a female partner of childbearing potential must use a male condom plus spermicide (except in countries where not approved), and it is highly recommended for the female partner of a male patient to also use a highly effective method of contraception
- Restriction of blood donation timelines post study treatment updated

### **Section 3.9 Discontinuation of IP**

The stipulation for discontinuation of IP of any AE that meets the criteria for discontinuation was removed.

Following discontinuation criteria added to be in line with Toxicity Management guidelines.

Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Appendix F) or as defined in the local prescribing information for the SoC agent.

### **Section 4 Study plan and timing of procedures**

Descriptions of assessment timing for all treatment arms and for immunotherapy and SoC treatment arms were added before all the tables of Schedules of Assessments to clarify dosing delays and subsequent assessments.

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

- The window for Cycle 1 was amended from +1 to +3 days
- Activated partial thromboplastin time (APTT) and international normalized ratio (INR) assessments, which will be performed as clinically indicated and at Screening, were added to the table
- sPD-L1 (serum), Circulating soluble factors, SNP genotyping, PaxGene-RNA and PGx research testing has been removed as these are no longer applicable
- For the pharmacokinetic samples, it is now specified that they will take place on the same day as the infusion and within 1 hour of end of infusion, as opposed to up to 1 hour pre-dose and with 10 minutes of the end of the infusion
- Clinical chemistry, hematology, TSH, free T3, and free T4 and Urinalysis can be performed within 3 days prior to randomization there is no need to repeat the same on the day of randomization. Hence, footnote 'd' has been added to these tests
- Foot notes are also updated

## **Section 5.1 Efficacy Assessments**

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

Also it was clarified that confirmatory scan should occur preferably at the next regularly scheduled imaging visit (based on randomization date).

### **Section 5.2.1 Laboratory safety assessments**

- In Table 5, provision is made that if the amylase and lipase analysis could not be performed in a local laboratory, then 1 or the other would be performed in line with local practice
- Table 5 is also updated with additional test in line with study plan and procedures. Also, footnotes are updated to clarify timing and requirement of the tests
- Table 6 was revised to remove the following hematology tests: Basophils, Eosinophils, Hematocrit, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin concentration Mean Corpuscular Volume and Red Blood Cells count because these are unnecessary for safety and to reduce the amount of blood drawn from the patients. Laboratory assessments that are not necessary to monitor safety based on the toxicity profile of the IP or SoC arms were removed to reduce patient burden
- In Table 6, APPT and INR are added to the table, and it is stipulated that they will be assessed at Screening rather than Baseline as indicated in the table footnote
- Chemistry panel timing post study drug discontinuation clarified

### **Section 5.2.4 Vital signs**

- Blood pressure may now be measured in a supine or semi-supine position rather than just a supine position. Monitoring of patient at first infusion and subsequent infusions are clarified
- Also, it was clarified vital collection based on first infusion and subsequent infusion

### **Section 5.3.2 Other safety assessments**

This new section has been added to closely monitor new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease.

### **Section 5.4 Pharmacokinetics and Section 5.5 Biomarker Analysis**



Storage of samples updated to add that sample will also be stored in AstraZeneca designated Biobank.

### **Section 5.4.3 Storage and destruction of pharmacokinetic/ADA samples and 5.5.5 Chain of custody of biological samples**

It has been clarified that Sample will be retained at AstraZeneca designated biobanks as well.

Also, storage duration for MEDI4736 & TREME PK and ADA samples should be changed to “a maximum of 15 years after the study ends” in order to harmonize the storage duration for all the samples.

### **Section 5.5.1 Collection of patient samples for stratification by PD-L1**

Tumor storage location has been clarified that tumor will be retained at CCI [REDACTED].

Also clarified that patients with a single target lesion, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.

### **Section 5.5.2 Exploratory Biomarkers**

Relevant section related to SNP Genotyping, PGx research, PaxGene-RNA & circulating soluble factors removed as these are no longer applicable.

## **Section 6 Safety reporting and medical management**

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

6.1 Definition of serious adverse events

6.2 Recording of adverse events

6.3 Definition of adverse events

**to**

6.1 Definition of adverse events

6.2 Definition of serious adverse events

6.3 Recording of adverse events

Time period of recording adverse events after last dose of both arms updated.

## **Section 6.1 Definition of adverse events**

Definition of adverse events of adverse event updated to clarify that progression of the malignancy under evaluation should not be considered as adverse event.

### **Section 6.1.2 Relationship to protocol procedures**

This section was revised to add “prior to administration of IP or SoC” into the parenthetical about SAEs that occur prior to the administration of IP to provide clarity on the non-treatment emergent SAEs.

### **Section 6.1.8 Deaths**

In accordance with MEDI4736 and Tremelimumab protocol template deaths are to be reported to monitor or physician instead only to physician.

New requirement of death related SAE collection timelines are updated. This is added to monitor the late onset of drug related SAEs.

### **Section 6.6.2 Paternal Exposure**

Timelines of follow-up and documentation of pregnancy outcome are updated.

## **Section 7.1 Identity of investigational product(s)**

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

## **Section 7.3 Labeling, Section 10.3 Ethics and regulatory review and Section 10.5 Changes to the protocol and informed consent form**

Japan specific wordings added.

## **Section 7.7 Concomitant and other treatments**

This section revised for clarity and to include collection of data timelines for safety purposes including the table of prohibited medication/class of drug was revised based on the updated information available on prohibited and concomitant medications.

## **Section 7.8 Post study access to study treatment**

Wording related to 12 months treatment removed as patient can continue more than 12 months treatment based on investigator discretion.

## **Section 8.4.1 Calculation or derivation of efficacy variables**

Secondary analysis of OS in PD-L1 negative is included.

### **Section 8.4.1.2 Progression-free survival**

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

### **Section 8.4.2.1 Adverse events**

This section updated with AE recording timelines.

### **Appendix C Pharmacogenetics Research**

Storage location of link between the patient enrollment/randomization code and the DNA number has been updated.

### **Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)**

Has been updated to clarify on the target lesions, use of scans with IV contrast, and use of FDG-PET/CT scans against dedicated diagnostic contrast-enhanced CT scans. Also, criteria for progression as per RECIST has been further clarified.

Central review section of this appendix is also updated to clarify that contract research organization appointed by AstraZeneca is responsible for providing necessary document for image collection and transfer. However, management of patients will be based solely upon the local assessments conducted by the investigator.

### **Appendix F Management of investigational product-related toxicities, and Appendices**

Appendix F was updated with the new version of the Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-related, and Nonimmune-mediated Reactions (MEDI4736 Monotherapy, Tremelimumab Monotherapy, or MEDI4736 + Tremelimumab Combination Therapy).

Also a sentence added to clarify that guidelines are prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities.

Also, MEDI4736 + tremelimumab and MEDI4736 monotherapy adverse events of special interest (AESI) of Appendix F was updated to reduce the emphasis on MEDI4736 and tremelimumab's biochemical properties in relation to AESIs, and also to remove the explanation of MEDI4736's main AESIs and refer the reader to the current IB where these are explained in full, together with specific guidelines for their evaluation and treatment.

**Version 3, 21 August 2015**

Changes to the protocol are summarized below.

Appendix G has been updated based on new guidelines to Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy) July 2<sup>nd</sup>, 2015. Details of changes to the protocol are summarized in Amendment 2.

**Version 2, 06 August 2015**

Changes to the protocol are summarized below.

CSP amended to clarify the inclusion and exclusion criteria. Also, study assessments were clarified. Details of changes to the protocol are summarized in Amendment 1.

**Version 1, 11 June 2015**

Initial Version

## PROTOCOL SYNOPSIS

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

---

#### **International Coordinating Investigator**

PPD

01246-000 – São Paulo – SP, Brazil

Tel.: PPD

#### **Study site(s) and number of patients planned**

The study will enroll approximately 1330 patients to identify approximately 800 patients who will be randomized to receive MEDI4736 + tremelimumab combination therapy or platinum-based Standard of Care (SoC) therapy (400 patients in each group, including approximately 336 patients with programmed cell death ligand 1 [PD-L1]–positive non-small-cell lung cancer [NSCLC], defined as PD-L1 tumoral expression  $\geq 25\%$ ). Global recruitment will be complete once approximately 800 patients have been randomized of which 30 patients are from mainland China. Once global enrollment is completed, the recruitment will continue in mainland China only. A total of approximately 160 patients from mainland China will be randomized (refer to section 8.6 for more details).

---

| <b>Study period</b>   | <b>Phase of development</b> |     |
|---|-----------------------------|-----|
| Estimated date of first patient enrolled                                  | Q3 2015                     | III |
| Estimated date of last patient last visit for final analysis of the study | Q3 2020                     | III |

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#### **Study design**

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

Patients will provide a tumor tissue sample at enrolment to determine PD-L1 expression status (defined by the **CCI**). Mutation assessments for blood tumor mutational burden (bTMB) will be performed on **CCI**.

- $\geq 20$  mut/Mb tumor mutational burden in blood is considered as bTMB high
- $< 20$  mut/Mb tumor mutational burden in blood is considered as bTMB low
- $\geq 25\%$  PD-L1 and  $\geq 1\%$  PD-L1 membrane expression in tumoral tissue are considered as relevant positive sub-groups
- $< 25\%$  PD-L1 is considered low/negative
- $< 1\%$  PD-L1 is considered negative

For clarity, these subgroups are referred to hereafter as patients with PD-L1-positive $_{25\%}$ , PD-L1-positive $_{1\%}$ , PD-L1-low/negative or PD-L1-negative tumors, respectively).

Patients will be randomized in a 1:1 ratio in a stratified manner according to PD-L1 tumor expression status (PD-L1-positive $_{25\%}$  versus PD-L1-low/negative), histology (squamous versus non-squamous), and smoking status (never smoker versus ever smoker) to receive treatment with MEDI4736 + tremelimumab combination therapy or SoC therapy.

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

Global recruitment will be complete once approximately 800 patients have been randomized of which 30 patients are from mainland China. Once global enrollment is completed the recruitment will continue in mainland China only. A total of approximately 160 patients from mainland China will be randomized (refer to Section 8.6 for more details). This is to ensure adequate Chinese patient participation to satisfy China health authority requirements to evaluate consistency in safety and efficacy of MEDI4736 + tremelimumab in Chinese patients with advanced or metastatic EGFR and ALK wild-type NSCLC.

## Objectives

All objectives will be evaluated for all patients, unless otherwise indicated. The primary objective is assessment of overall survival (OS) in patients with bTMB  $\geq 20$ mut/Mb.

| Primary objectives:   | Outcome measures: |
|---|-------------------|
| To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of Overall survival (OS) in patients with bTMB $\geq 20$ mut/Mb. | OS                |

| Secondary objectives:  | Outcome measures:   |
|--|---|
| To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS   | OS in patients with <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 16mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math>12 mut/Mb NSCLC</li> <li>• PD-L1-negative NSCLC</li> <li>• All patients with NSCLC</li> <li>• bTMB &lt; 20 mut/Mb NSCLC</li> <li>• bTMB non-evaluable population</li> </ul>   |
| To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS, ORR, DoR, OS12, OS18, OS24, APF12, and PFS2 | PFS, ORR, DoR and APF12 using Investigator assessments according to RECIST 1.1 in patients with <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 20mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 16mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 12mut/Mb NSCLC</li> <li>• PD-L1 negative NSCLC</li> <li>• All patients with NSCLC</li> </ul> PFS2 using local standard clinical practice <sup>a</sup> , OS12, OS18 and OS24 in patients with <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 20mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 16mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 12mut/Mb NSCLC</li> <li>• PD-L1 negative NSCLC</li> <li>• All patients with NSCLC</li> </ul> |
| To assess efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of ORR, PFS and OS in further PD-L1 defined populations         | OS in patients with PD-L1 TC $\geq$ 25% and PD-L1 TC $\geq$ 50%<br><br>PFS and ORR using Investigator assessments according to RECIST 1.1 in patients with PD-L1 TC $\geq$ 25% and PD-L1 TC $\geq$ 50%.   |
| To further assess efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of ORR, PFS and OS (including OS12, OS18 and OS24)      | OS in patients in analysis sets defined by tTMB cutoffs.<br><br>PFS and ORR using Investigator assessments according to RECIST 1.1 in patients in analysis sets defined by tTMB cutoffs <sup>b</sup> .  |

| <b>Secondary objectives:</b>   | <b>Outcome measures:</b>  |
|--|---|
| To assess the pharmacokinetics (PK) of MEDI4736 + tremelimumab combination therapy | Concentration of MEDI4736 and tremelimumab in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling) |
| To investigate the immunogenicity of MEDI4736 and tremelimumab                     | Presence of anti-drug antibodies (ADAs) for MEDI4736 and tremelimumab (confirmatory results: positive and negative; titers)                                     |

<sup>a</sup> PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint, or death

<sup>b</sup> tTMB cutoffs will be defined in the SAP ahead of the DBL from a dataset independent of data collected in this study.

| <b>Safety objective:</b>  | <b>Outcome measures:</b>  |
|---|---|
| To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy compared to SoC in the first-line setting for treatment of advanced or metastatic NSCLC patients | Adverse events (AEs), physical examinations, laboratory findings, and vital signs |

An objective to meet China Health Authority requirement is to evaluate consistency in efficacy and safety among Chinese patients for benefit-risk assessment of MEDI4736 + tremelimumab combination therapy compared to SoC. Further details regarding the Chinese specific analysis, please refer the China specific SAP.

### **Target patient population**

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

### **Duration of treatment**

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

### **Progression during treatment**

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

Patients in the immunotherapy arm with PD according to RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive



their assigned treatment for as long as they are gaining clinical benefit. However, patients in the immunotherapy group will not be permitted to continue immunotherapy if progression occurs after confirmed response [CR defined as CR or PR as defined by RECIST 1.1] to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions) i.e., the response and then the progression events both occurred in the target lesions while the patient was receiving immunotherapy during the same treatment period.

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

### **Follow up of patients post discontinuation of study drug**

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

### **Survival**

All patients randomized in the study should be followed up for survival.

### **Post Data Cut Off (DCO)**

For patients continuing to receive MEDI4736 or MEDI4736 + tremelimumab treatment following the scheduled DCO for final analysis of the global cohort, it is recommended that the patients continue the scheduled site visits. For those patients from China who are in the Global cohort, final DCO and DBL will be when the China cohort conducts its final DCO and final DBL.

Based on the analysis results of the global cohort, a decision was made to move the following patients of global cohort to a roll over study

- Patients who are still receiving study treatment (MEDI4736/tremelimumab treatment)
- Patients who were receiving study treatment (MEDI4736/tremelimumab treatment) and are now being followed up for survival

No further data collection in to the Neptune study database is required until the patients in global cohort (with the exception of patients from China) are transitioned to a roll over study. Survival data of patients who are ongoing on MEDI4736/tremelimumab treatment or in follow up after discontinuation of the MEDI4736/tremelimumab treatment, should be documented in patient records. Upon enrolment into the roll over study these data may be retrieved.

All SAEs that occur in patients still receiving MEDI4736/tremelimumab treatment (or within the 90 days following the last dose of MEDI4736/tremelimumab treatment) post the final DCO and database closure must be reported as detailed in Section [6.4](#)

Patients moving to the roll over study will require a new Informed Consent. The OS data collected in the roll over study may be combined with the OS data from NEPTUNE and evaluated as a combined dataset.

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

### MEDI4736 + tremelimumab combination therapy

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

### Standard of Care therapy

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

- Paclitaxel + carboplatin: Paclitaxel 200 mg/m<sup>2</sup> and carboplatin area under the curve (AUC) 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m<sup>2</sup> via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m<sup>2</sup> via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m<sup>2</sup> via IV infusion on Days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Pemetrexed + cisplatin (non-squamous patients only): Pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy
- Pemetrexed + carboplatin (non-squamous patients only): Pemetrexed 500 mg/m<sup>2</sup> and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy

## **Statistical methods**

The primary objectives of this study are to assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with SoC in terms of overall survival (OS) in patients with EGFR and ALK wild type advanced or metastatic NSCLC and bTMB  $\geq$  20 mut/Mb. OS will

be defined as the time from the date of randomization until death due to any cause. Secondary efficacy variables include OS in patients with bTMB  $\geq 16$  mut/Mb, bTMB  $\geq 12$  mut/Mb, PD-L1-negative tumours, all-comers FAS population, bTMB  $< 20$  mut/Mb, and bTMB non-evaluable population, as well as progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), proportion of patients alive and progression free at 12 months from randomization (APF12), proportion of patients alive at 12 months from randomization (OS12), proportion of patients alive at 18 months from randomization (OS18), proportion of patients alive at 24 months from randomization (OS24), and time from randomization to second progression (PFS2) in patients with bTMB  $\geq 20$  mut/Mb, bTMB  $\geq 16$  mut/Mb, bTMB  $\geq 12$  mut/Mb, PD-L1-negative tumours and the all-comers FAS population. All tumor-assessment-related endpoints are as per Investigator assessments. OS, PFS and ORR will also be evaluated in patients with PD-L1 TC  $\geq 25\%$  and TC  $\geq 50\%$ , and in analysis sets defined by tTMB cutoffs.

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

Approximately 800 patients will be randomized globally 1:1 to MEDI4736 + tremelimumab combination therapy or SoC (including approximately 336 patients with PD-L1-positive<sub>25%</sub> NSCLC, and approximately 520 patients with PD-L1-positive<sub>1%</sub> NSCLC). The randomization will be stratified based on PD-L1 tumor expression status ( $\geq 25\%$  versus  $< 25\%$ ), histology (squamous versus non-squamous), and smoking status (never smoker versus ever smoker).

A hypothesis of improved OS will be tested in the bTMB  $\geq 20$  mut/Mb population when there is (approximately) 87% maturity in the bTMB  $\geq 20$  mut/Mb population.

With a 12-month recruitment period and a minimum follow up period of 43 months assumed, it is anticipated that this analysis will be performed 55 months after the first patient has been recruited.

### **MEDI4736 + tremelimumab versus SoC (OS in bTMB $\geq 20$ mut/Mb population)**

Assuming the true OS average hazard ratio (HR) is 0.49 and the median OS in SoC chemotherapy alone arm is 10 months following an exponential distribution for both MEDI4736 + tremelimumab and SoC arm in the bTMB $\geq 20$  mut/Mb population, with approximately 140 patients, 122 OS events from the global cohort (approximately 87% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha overall level of 5%. The smallest treatment difference that is statistically significant will be an HR of 0.70.

A HR of 0.49 is based on observation from D419AC00001 study, as well as based on what would be considered a clinically meaningful improvement in the biomarker selected population.

No interim analysis is planned.

OS and PFS will be analyzed using a log-rank test. The effect of treatment will be estimated by the HR together with appropriately sized confidence interval and p-value.

Safety data will be summarized descriptively and will not be formally analyzed.

### **China data**

Global recruitment will be complete once approximately 800 patients have been randomized of which 30 patients are from mainland China. Once global enrollment is completed, the recruitment will continue in mainland China only. A total of approximately 160 patients from mainland China will be randomized (refer to Section 8.6 for more details). Details of the analysis for China will be detailed in the China specific SAP. The data cut-off for the China cohort analysis may be different from the global data cut-off to ensure an appropriate evaluation. Safety and tolerability will be summarized for the China Safety Analysis Set.

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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.

| <b>Abbreviation or special term</b> | <b>Explanation</b>  |
|-------------------------------------|---|
| ADA                                 | Anti-drug antibody  |
| AE                                  | Adverse event   |
| ALK                                 | Anaplastic lymphoma kinase  |
| ALT                                 | Alanine aminotransferase  |
| APF12                               | Proportion of patients alive and progression free at 12 months from randomization |
| APTT                                | Activated Partial Thromboplastin time   |
| AST                                 | Aspartate aminotransferase  |
| AUC                                 | Area under the plasma drug concentration-time curve                               |
| AUC <sub>ss</sub>                   | Area under the plasma drug concentration-time curve at steady state               |
| BoR                                 | Best objective response   |
| BP                                  | Blood pressure  |
| C                                   | Cycle   |
| CD                                  | Cluster of differentiation  |
| CI                                  | Confidence interval   |
| CL                                  | Clearance   |
| C <sub>max</sub>                    | Maximum plasma concentration  |
| C <sub>max,ss</sub>                 | Maximum plasma concentration at steady state                                      |
| CR                                  | Complete response   |
| CSA                                 | Clinical study agreement  |
| CSR                                 | Clinical Study Report   |
| CT                                  | Computed tomography   |
| CTCAE                               | Common Terminology Criteria for Adverse Event                                     |
| CTLA-4                              | Cytotoxic T-lymphocyte-associated antigen 4                                       |
| C <sub>trough,ss</sub>              | Trough concentration at steady state  |
| CXCL                                | Chemokine (C-X-C motif) ligand  |
| D5W                                 | 5% dextrose in water  |
| DoR                                 | Duration of response  |
| DNA                                 | Deoxyribonucleic acid   |

| <b>Abbreviation or special term</b> | <b>Explanation</b>  |
|-------------------------------------|---|
| EC                                  | Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee |
| ECG                                 | Electrocardiogram   |
| ECOG                                | Eastern Cooperative Oncology Group  |
| eCRF                                | Electronic case report form   |
| EDoR                                | Expected duration of response   |
| EGFR                                | Epidermal growth factor receptor  |
| EU                                  | European Union  |
| FAS                                 | Full analysis set   |
| FDA                                 | Food and Drug Administration  |
| GCP                                 | Good Clinical Practice  |
| GI                                  | Gastrointestinal  |
| GMP                                 | Good Manufacturing Practice   |
| HBsAg                               | Hepatitis B surface antigen   |
| HBV                                 | Hepatitis B virus   |
| hCG                                 | Human chorionic gonadotropin  |
| HIV                                 | Human immunodeficiency virus  |
| HR                                  | Hazard ratio  |
| IB                                  | Investigator's Brochure   |
| IC                                  | Immune Cells  |
| ICF                                 | Informed consent form   |
| ICH                                 | International Conference on Harmonization   |
| IDMC                                | Independent Data Monitoring Committee   |
| IFN                                 | Interferon  |
| IgG                                 | Immunoglobulin G  |
| IHC                                 | Immunohistochemistry  |
| IL                                  | Interleukin   |
| ILD                                 | Interstitial lung disease   |
| IM                                  | Intramuscular   |
| imAE                                | Immune- mediated adverse event  |
| IMT                                 | Immunomodulatory therapy  |
| INR                                 | International normalized ratio  |

| <b>Abbreviation or special term</b> | <b>Explanation</b>  |
|-------------------------------------|---|
| IP                                  | Investigational product   |
| IRB                                 | Institutional Review Board  |
| ITT                                 | Intent-to-Treat   |
| IV                                  | Intravenous   |
| IVRS                                | Interactive Voice Response System                                     |
| IWRS                                | Interactive Web Response System                                       |
| LFT                                 | Liver function test   |
| mAb                                 | Monoclonal antibody   |
| MedDRA                              | Medical Dictionary for Regulatory Activities                          |
| MHLW                                | Minister of Health, Labor, and Welfare                                |
| miRNA                               | Micro-ribonucleic acid  |
| MRI                                 | Magnetic resonance imaging  |
| MTP                                 | Multiple testing procedure  |
| NCI                                 | National Cancer Institute   |
| NE                                  | Not evaluable   |
| NOS                                 | Not otherwise specified   |
| NSCLC                               | Non–small-cell lung cancer  |
| NTL                                 | Non-target lesion   |
| OAE                                 | Other significant adverse event                                       |
| ORR                                 | Objective response rate   |
| OS                                  | Overall survival  |
| PD                                  | Progressive disease   |
| PD-1                                | Programmed cell death 1   |
| PD-L1                               | Programmed cell death ligand 1  |
| PD-L1 positive <sub>25%</sub>       | ≥25% of tumor cells with membrane staining for PD-L1 at any intensity |
| PD-L1-positive <sub>1%</sub>        | ≥1% of tumor cells with membrane staining for PD-L1 at any intensity  |
| PD-L1-low/negative                  | <25% of tumor cells with membrane staining for PD-L1 at any intensity |
| PD-L1-negative                      | <1% of tumor cells with membrane staining for PD-L1 at any intensity  |
| PD-L2                               | Programmed cell death ligand 2  |
| PFS                                 | Progression-free survival   |
| PFS2                                | Time from randomization to second progression                         |
| PK                                  | Pharmacokinetic(s)  |

---

| <b>Abbreviation or special term</b> | <b>Explanation</b>   |
|-------------------------------------|--|
| PR                                  | Partial response   |
| q2w                                 | Every 2 weeks  |
| q3w                                 | Every 3 weeks  |
| q4w                                 | Every 4 weeks  |
| q6w                                 | Every 6 weeks  |
| q8w                                 | Every 8 weeks  |
| RECIST 1.1                          | Response Evaluation Criteria in Solid Tumors, Version 1.1    |
| RNA                                 | Ribonucleic acid   |
| RR                                  | Response rate  |
| RT-QPCR                             | Reverse transcription quantitative polymerase chain reaction |
| SAE                                 | Serious adverse event  |
| SAP                                 | Statistical Analysis Plan                                    |
| SAS                                 | Safety analysis set  |
| SD                                  | Stable disease   |
| SNP                                 | Single nucleotide polymorphism                               |
| SoC                                 | Standard of Care   |
| sPD-L1                              | Soluble programmed cell death ligand 1                       |
| T <sub>3</sub>                      | Triiodothyronine   |
| T <sub>4</sub>                      | Thyroxine  |
| TL                                  | Target lesion  |
| TMB                                 | Tumor mutational burden                                      |
| tTMB                                | Tissue tumor mutational burden                               |
| bTMB                                | Blood tumor mutational burden                                |
| TSH                                 | Thyroid-stimulating hormone                                  |
| ULN                                 | Upper limit of normal  |
| US                                  | United States  |
| WBDC                                | Web-Based Data Capture                                       |
| WHO                                 | World Health Organization                                    |

---

## 1. INTRODUCTION

### 1.1 Background and rationale for conducting this study

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

Despite advances in the diagnosis, imaging, staging, and treatment of NSCLC, the estimated overall 5-year survival for patients in Europe and the United States (US) continues to be low (11% and 17%, respectively; [D'Addario et al 2010](#), [Howlander et al 2014](#)). Patients presenting with advanced NSCLC have a median overall survival (OS) of 10 to 12 months ([Ayers et al 2017](#), [Balar et al Dec 2017](#), [Bonomi 2010](#)). Patients without a targetable mutation (i.e., epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] mutation) demonstrate responses to systemic treatment of approximately 20% to 30% and progression-free survival (PFS) of 4 to 5 months ([Scagliotti et al 2008](#), [Schiller et al 2002](#)). The duration of responses (DoRs) is also limited, and toxicities can be a major limiting factor. The 1-year survival rate is 30% to 40% for patients with a good performance status. Maintenance therapy, with either continuation or switch, has also been recommended for certain histologic subtypes of NSCLC; for example, maintenance with pemetrexed has been shown to improve OS and PFS, particularly in non-squamous histologies ([Carbone et al 2017](#), [Ciuleanu et al 2009](#), [Paz-Ares et al 2013](#)).

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

#### 1.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors ([Dunn et al 2004](#)).

PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor ([Johnson et al 2016](#), [Keir et al 2008](#)) and to CD80 ([Butte et al, 2007](#)). PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by

the immune system. In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. Binding of CTLA-4 to CD80 or CD86 on IC leads to inhibition of T-cell activation (Fife and Bluestone, 2008). Expression of PD-L1 protein on both tumor cells (TC) and tumor infiltrating IC is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFN $\gamma$ ). The binding of PD L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, protecting the tumor from immune elimination (Zou and Chen 2008). PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated (Butte et al, 2007; Paterson et al, 2011).

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

In vivo studies have shown that MEDI4736 inhibits tumor growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015).

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012; Hirano et al 2005; Iwai et al 2002; Okudaira et al 2009; Topalian et al 2012; Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al, 2014; Rizvi et al 2015; Segal et al 2015).

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife and Bluestone, 2008). Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies



whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there is data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

However, PD-L1 expression alone does not appear to fully explain the OS benefit seen in patients treated with these drugs (Reck et al 2014, Carbone et al 2017, Hui et al 2017). Increasing evidence suggests the overall number of mutations of NSCLC tumors shape their immunogenicity and can also influence the response to immunotherapies. Tumor mutational burden (TMB), defined as the number of nonsynonymous somatic mutations within a tumor's genome and characterised from tumor tissue (tTMB) or from circulating tumor DNA in blood (bTMB) is an encouraging and important predictive biomarker for immune checkpoint inhibitor treatment. Multiple studies have shown that TMB may be a surrogate for overall neoantigen frequency (Rizvi et al 2015, Rooney et al 2015). High neoantigen frequency has been associated with upregulation of effector T cells in the tumor microenvironment. Immune checkpoint inhibitors by their ability to block negative regulatory signals to T cells, likely enhance this neoantigen specific T cell reactivity. This theory has been supported by multiple publications across tumor types, immune checkpoint inhibitor treatments and lines of treatment. The first published study of TMB as a biomarker of clinical outcomes demonstrated efficacy in metastatic melanoma with anti-CTLA-4 therapy (Snyder, A. et al 2014). A subsequent study in NSCLC reported improved survival with PD-1 and CTLA-4 inhibitors in tumors enriched for clonal neoantigens (Rizvi et al 2015). Recently, a retrospective analysis of two large datasets with anti-PD-L1 therapy in metastatic NSCLC explored a range of bTMB cut-points that correlated to clinically meaningful improvements in overall survival (Gandara et al 2018). Interim data with the same PD-L1 inhibitor suggested patients with high bTMB (defined as  $\geq 14.5$  mut/Mb), trended to a PFS benefit (Vamsidhar Velcheti et al 2018, E S Kim et al 2018). Two additional clinical trials with a PD-1 inhibitor in combination with a CTLA-4 inhibitor demonstrated better clinical outcomes in patients with high tTMB (defined as  $\geq 10$  mut/Mb) with both squamous and non-squamous NSCLC (Hellmann et al 2018). The observed association of TMB with improved survival with ICI treatment has also been examined more broadly in an analysis involving a range of advanced tumor histologies. This analysis found that overall survival was better for patients with higher levels of TMB (highest 20% in each histology). (Samstein et al 2019).

Published data with MEDI4736 in combination with tremelimumab also support the hypothesis that high TMB can be predictive of clinical outcomes. Tumor tissue from Study CCI [REDACTED], a phase 1b study of patients with NSCLC, analysed tTMB in patients with non-squamous histology and reported median PFS of 7.1m (1.7m-9.1m) in patients with tTMB high (defined as  $\geq 11.41$  mut/Mb) vs 1.7m (1.6m-3.6m) in patients with tTMB low (Higgs BW et al 2018).

In Study D419AC00001 a study of MEDI4736 with or without tremelimumab vs standard of

care platinum doublet chemotherapy, in patients with Stage IV NSCLC, bTMB was evaluated as a prespecified exploratory analysis. bTMB was evaluated with the CCI [REDACTED] and the analysis comprised the largest dataset to date with over 800 patients in the bTMB evaluable set. Both the MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab arms demonstrated clinically meaningful efficacy compared to SoC in TMB high patients defined by a range of TMB cut-points, however the effect observed in the combination therapy arm was consistently greater compared to the monotherapy arm. In patients with high bTMB (defined as  $\geq 16$ mut/Mb), combination immunotherapy when compared with SoC demonstrated a median OS of 16.5m vs 10.5m, HR 0.62 (95% CI 0.451-0.855) and survival rate at 24months was 39% vs 18%, respectively (Rizvi et al 2018). In the subgroup, TMB  $\geq 12$ mut/Mb, the HR of D+T vs SoC was 0.65 (95% CI 0.50-0.84) (Peters et al 2019). D+T vs SoC in the exploratory PD-L1 negative population also demonstrated improved outcomes with D+T (HR 0.73, 95% CI 0.512-1.041) (Rizvi et al 2018).

In patients with bTMB  $\geq 20$ mut/Mb, the survival benefit was even more pronounced: HR 0.49 (95% CI 0.32,0.74) with combination therapy vs SoC and the 24month survival rate was 48.1% (95% CI 35.5, 59.7) in the combination therapy arm. The 24 month survival rate for SoC was 19.4%, for MEDI4736 monotherapy was 33.8% (95% CI 23.4, 44.5) and MEDI4736 vs SoC demonstrated HR0.72 (95% CI 0.50, 1.05) (Peters et al 2019)

These data not only supports the hypothesis that bTMB can be considered as a predictive marker for clinical outcomes including OS and PFS, it also provides evidence of the additive effect of CTLA-4 inhibition by tremelimumab in the subset of patients with increased mutational burden. The totality of the data suggests that TMB is a biomarker of clinical efficacy for immunotherapy and perhaps more useful as a biomarker than PD-L1 when considering anti-PD-L1/PD-1 in combination with anti-CTLA-4 therapy.

### 1.1.2 MEDI4736

MEDI4736 is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It 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.) MEDI4736 has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN) (Stewart et al 2015). To date MEDI4736 has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of MEDI4736 monotherapy are summarized in Section 1.3.2.1 and Toxicity Management Guideline (please see section 6.10). Refer to the current MEDI4736 Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

### **1.1.3 Tremelimumab**

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]- $\gamma$ ) from human T cells, peripheral blood mononuclear cells and whole blood ([Tarhini and Kirkwood 2008](#)). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.2. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

### **1.1.4 MEDI4736 in combination with tremelimumab**

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant, targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity ([Pardoll 2012](#)); therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications AstraZeneca is also investigating the use of MEDI4736 + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/pharmacodynamics, and preliminary antitumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is MEDI4736 every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 800 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of MEDI4736 + tremelimumab combination therapy are summarized in Sections 1.2.1.1 and 1.3.2.3. Refer to the current editions of the MEDI4736 and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

### **1.1.5 Rationale for conducting this study**

Current therapies for advanced NSCLC have poor outcomes (low 5-year survival of 17% for the US), with responses to systemic chemotherapy in the first-line setting of approximately 20% to 30%, and a median OS of approximately 10 to 12 months ([Ayers et al 2017](#), [Balar et al Dec 2017](#), [Bonomi 2010](#), [D'Addario et al 2010](#), [Scagliotti et al 2008](#), [Schiller et al 2002](#)). Responses are also limited in duration. Systemic chemotherapy is associated with significant side effects, including neutropenia, nausea, vomiting and dehydration, and alopecia ([Rosenberg et al 2016](#), [Sandler et al 2006](#), [Scagliotti et al 2008](#)). There is still a significant

unmet medical need for additional treatment options for use in this patient population as the 1-year survival rate is 30% to 40%.

As an antibody that blocks the interaction between PD-L1 and its receptors, MEDI4736 may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of antitumor 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](#), [Garon et al 2015](#), [Gettinger et al 2015](#), [Topalian et al 2012](#)). Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In addition, MEDI4736 monotherapy has shown durable responses in NSCLC in Study 1108 (see Section 1.3.1.1).

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

Based on the preliminary clinical efficacy and safety data observed in patients with NSCLC in Study D4190C00006 (with MEDI4736 + tremelimumab combination therapy), AstraZeneca plans to determine the activity of MEDI4736 in combination with tremelimumab as first-line treatment in patients with NSCLC. The preliminary efficacy, safety, and tolerability data of the MEDI4736 + tremelimumab combination in Study D4190C00006 support the development of these treatments in NSCLC. The primary endpoints of this Phase III study are to determine the OS benefit of MEDI4736 + tremelimumab combination therapy compared to Standard of Care (SoC) in patients with EGFR and ALK wild-type NSCLC when used as first-line treatment in patients with bTMB  $\geq$  20mut/Mb.

## **1.2 Rationale for study design, doses, and control groups**

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

### **1.2.1 MEDI4736 + tremelimumab dose and treatment regimen justification**

#### **1.2.1.1 MEDI4736+ tremelimumab combination therapy dose rationale**

The MEDI4736 + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of MEDI4736 and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

### **Pharmacokinetics/Pharmacodynamics data**

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of MEDI4736 in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from MEDI4736 monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state ( $AUC_{ss}$ ; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with MEDI4736. The observed MEDI4736 PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of MEDI4736 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when MEDI4736 and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state ( $C_{max,ss}$ ) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ( $C_{trough,ss}$ ) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with MEDI4736 monotherapy. There was evidence of augmented pharmacodynamic activity relative to MEDI4736 monotherapy with combination doses containing 1 mg/kg tremelimumab, including both the 15 and 20 mg/kg MEDI4736 plus 1 mg/kg tremelimumab combinations.

### **Clinical data**

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of MEDI4736 ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst MEDI4736 was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the risk:benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab and 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohorts treated at the Q2W schedule, the number of patients reporting any AE,  $\geq$ Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohort than the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the Q4W regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis, colitis and other immune mediated events, were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with MEDI4736. As a result, all combination doses

utilizing either the 3 or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of MEDI4736 with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of MEDI4736 may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of MEDI4736.

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

Preliminary clinical activity of the MEDI4736 and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg MEDI4736 Q4W cohorts demonstrated objective responses at all doses of tremelimumab and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations.

All together, the data suggested that a 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current MEDI4736 Investigator's Brochure for a complete summary of non-clinical and clinical information on the MEDI4736 + tremelimumab combination, including safety, efficacy and pharmacokinetics.

#### **1.2.1.2 Rationale for 4 cycles of combination therapy followed by MEDI4736 monotherapy**

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up ([Schadendorf et al 2013](#)).

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

- Nivolumab (anti-PD-1) was dosed Q2W for up to 96 weeks in a large Phase I dose escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis ([Brahmer et al 2014](#), [Drake et al 2013](#), [Hodi et al 2014](#))

Similar long term results may be expected with use of other immune-mediated cancer therapeutics such as tremelimumab, MEDI4736, or the combination of the two agents.

The MEDI4736 + tremelimumab combination therapy will be administered for 4 doses followed by monotherapy MEDI4736 20 mg/kg q4w until disease progression or unless other specific discontinuation criteria are met.

### **1.2.2 Rationale for Standard of Care as a comparator**

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

### **1.2.3 Rationale for retreatment option**

In contrast to patients treated with chemotherapy, who are unlikely to respond to rechallenge with the same agent upon progression, responses have been observed upon retreatment with IMTs. Several potential mechanisms of resistance to IMT exist, including loss of T-cell “memory” or recurrence of immune escape, which suggest retreatment for patients who initially respond or demonstrate SD is reasonable. Preliminary data in patients previously treated with IMTs suggest that responses are similar to those observed following initial treatment ([Forde et al 2014](#), [Higgs et al 2017](#), [Hodi et al 2010](#)).

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

### **1.2.4 Rationale for endpoints**

The primary aim of this study is to determine the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS in patients with high bTMB, defined as bTMB  $\geq 20$ mut/Mb.

The secondary efficacy endpoints of OS in bTMB  $\geq 16$ mut/Mb, OS in bTMB  $\geq 12$ mut/Mb, OS in PD-L1 negative, OS in all patients, OS in bTMB  $< 20$  mut/Mb and bTMB non-evaluable, PD-L1 TC  $\geq 25\%$ , OS in PD-L1 TC  $\geq 50\%$ , OS in tTMB-based analysis sets, PFS, ORR, DoR and, proportion of patients alive at 12 months from randomization (OS12), proportion of patients alive at 18 months from randomization (OS18), proportion of patients alive at 24 months from randomization (OS24), proportion of patients alive and progression free at 12 months from randomization (APF12) and time from randomization to second

progression (PFS2) will be examined to further evaluate the antitumor effect and survival benefit of MEDI4736 + tremelimumab combination therapy versus SoC. PFS, ORR, DoR, and APF12 will be assessed using Investigator assessments according to RECIST 1.1.

The PK and immunogenicity of MEDI4736 and tremelimumab are being examined to assess the PK of both agents when administered in combination, and to assess their potential impact on PK, pharmacodynamics, and safety and efficacy parameters. Biological samples will be used to explore potential biomarkers in tumor, whole blood, plasma, and/or serum that may influence pathogenesis, response, and clinical characteristics.

### **1.3 Benefit/risk and ethical assessment**

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

#### **1.3.1 Potential benefits**

##### **1.3.1.1 MEDI4736**

The majority of the safety and efficacy data currently available for MEDI4736 are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Data from Study 1108 were presented at the European Society for Medical Oncology 2014 Congress. As of 21 August 2014, 162 patients with NSCLC were evaluable for response analysis. The disease control rate (DCR) at 12 weeks in patients receiving 10-mg/kg MEDI4736 q2w was 39%, and the ORR was 15% (26% [12 out of 47 patients] with known PD-L1-positive<sub>25%</sub> NSCLC [i.e.,  $\geq 25\%$  PD-L1 expression] and 10% [7 out of 74 patients] with known PD-L1-low/negative NSCLC [i.e.,  $< 25\%$  PD-L1 expression]). A total of 24% of patients receiving 10-mg/kg MEDI4736 q2w had SD for  $\geq 12$  weeks (including 21% [10 out of 47 patients] with known PD-L1-positive<sub>25%</sub> NSCLC and 32% [24 out of 74 patients] with known PD-L1-low/negative NSCLC). Responses were ongoing in 96% of responding patients with NSCLC receiving MEDI4736 10 mg/kg q2w, with an objective response duration ranging from 0.1 to 32.4 weeks ([Antonia et al 2014b](#)).

##### **1.3.1.2 MEDI4736 + tremelimumab combination therapy**

The preclinical and clinical justification for this combination as noted in Section 1.2.1 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma ([Wolchok et al 2013](#)). Further, preliminary efficacy data from Study D4190C00006 has demonstrated that this combination is clinically active and well tolerated. As of 27 January 2015, 53 patients were evaluable for response across various MEDI4736 + tremelimumab combination therapy dose regimens. Of these, 12 patients (23%) had a best response of PR and 14 patients (26%) had a best response of SD. In the 20-mg/kg MEDI4736 plus 1-mg/kg tremelimumab q4w cohort, a total of 5 of 11 patients were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with PR, 1 patient (20%) with SD, and 1 patient (20%) with



PD. (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

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

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

Given these findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1-positive tumors. Though biomarker development is ongoing and the final boundaries of these populations are yet to be established, there is also a potential unmet medical need in patients with PD-L1-low/negative tumors that needs to be addressed. Data, as of 27 January 2015 from Study 006 show that with the addition of tremelimumab to MEDI4736, the ORR can be increased to 25% (6 of 24 patients) in patients with PD-L1-low/negative NSCLC (as defined by the CCI [REDACTED]). As patients with PD-L1-positive tumors can also have an increase in ORR, from 25% (12 of 48 patients) with MEDI4736 monotherapy, to 36% with the combination of MEDI4736 and tremelimumab, the study will enroll all patients with NSCLC, with efficacy analysis performed in the overall study population, and pre-defined PD-L1 subgroups.

### 1.3.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

### **1.3.2.1 MEDI4736**

Risks with MEDI4736 include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g. Guillain Barre syndrome, myasthenia gravis).

For information on all identified and potential risks with MEDI4736 please always refer to the current version of the MEDI4736 IB.

In monotherapy clinical studies AEs reported at an incidence of > 20% include events such as fatigue, cough, decreased appetite, dyspnea and nausea. Approximately 10% of patients discontinued drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and CTC Grade 3 to 5 events reported across the MEDI4736 program.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. (Please refer to guidance in Section 6.10).

A detailed summary of MEDI4736 monotherapy AE data can be found in the current version of the MEDI4736 IB.

### **1.3.2.2 Tremelimumab**

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhea, enterocolitis, and intestinal perforation); endocrine disorders (hypo- and hyperthyroidism, hypophysitis, and adrenal insufficiency); skin effects (rash and pruritus); elevations in lipase and amylase and clinical manifestations of pancreatitis; hepatic events (including immune mediated hepatitis and liver enzyme elevations); pneumonitis and ILD; neurotoxicity (including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome); thrombocytopenia, anemia, and neutropenia; infusion-related reactions and hypersensitivity/anaphylactic reactions; renal events (including nephritis/autoimmune nephritis and acute kidney injury, autoimmune arthritis, Sjogren's syndrome, giant cell temporal arteritis and ulcerative colitis); hyperglycemia and diabetes mellitus.

For information on all identified and potential risks with tremelimumab, please always refer to the current version of the tremelimumab IB.

In monotherapy clinical studies, AEs reported at an incidence of  $\geq 20\%$  include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting and dyspnea.

Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab, and approximately 45% of patients experienced an SAE. Please see the current version of the IB for a detailed summary of monotherapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the tremelimumab program.

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

### **1.3.2.3 MEDI4736 + tremelimumab combination therapy**

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study D4190C00006 in patients with NSCLC, is being studied in a number of other ongoing clinical studies in a number of different indications and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20 mg/kg and a tremelimumab dose of 1 mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from Study D4190C00006, from other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab + tremelimumab combination, please always refer to the current version of the durvalumab IB.

In durvalumab + tremelimumab combination studies at the dose of durvalumab 20 mg/kg and tremelimumab 1 mg/kg, AEs reported at an incidence of > 20% included events such as fatigue, diarrhea, nausea, decreased appetite, pruritus, dyspnea, constipation and anemia. Please see the current version of the durvalumab IB for a detailed summary of combination therapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program, including durvalumab in combination with tremelimumab.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug, and approximately 16% of patients experienced an SAE that was related to durvalumab and tremelimumab by the study Investigator.

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

### **1.3.3 Overall benefit: risk and ethical assessment**

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

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

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, the activity seen with MEDI4736 and the MEDI4736 + tremelimumab combination therapy in this tumor type, and the strength of the scientific hypotheses under evaluation, the MEDI4736 + tremelimumab combination therapy proposed for evaluation in this study may have the potential to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable clinical responses, thereby potentially extending survival.

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

## 1.4 Study design

This is a randomized, open-label, multi-center, global Phase III study to determine the efficacy and safety of MEDI4736 + tremelimumab combination therapy versus platinum-based SoC chemotherapy in the first-line treatment of patients with EGFR and ALK wild-type advanced or metastatic NSCLC. Crossover from SoC to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy will not be permitted. A schematic diagram of the overall study design is shown in [Figure 1](#), and a detailed study flow chart is shown in [Figure 2](#).

This study will enroll approximately 1330 patients at sites in North America, Latin America, Asia, Europe, and Gulf countries to randomize approximately 800 patients (including approximately 336 patients with PD-L1-positive<sub>25%</sub> NSCLC) to treatment. Global recruitment will be complete once approximately 800 patients have been randomized of which 30 patients are from mainland China. Once global enrollment is completed, the recruitment will continue in mainland China only. A total of approximately 160 patients from mainland China will be randomized (refer to Section [8.6](#) for more details).

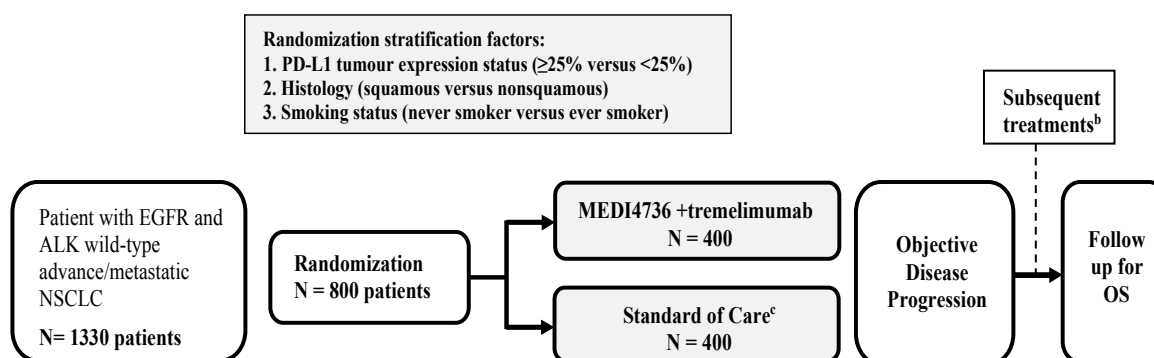
Patients will provide a tumor tissue sample at enrollment (newly acquired or archived sample <3 months old) to determine PD-L1 expression status (defined by the [CCI](#) [\[REDACTED\]](#)). Mutation assessments for blood tumor mutational burden (bTMB) will be performed on the [CCI](#) [\[REDACTED\]](#).

- $\geq 20$  mut/Mb tumor mutational burden in blood is considered as bTMB high
- $< 20$  mut/Mb tumor mutational burden in blood is considered as bTMB low
- $\geq 25\%$  PD-L1 and  $\geq 1\%$  PD-L1 membrane expression in tumoral tissue are considered as relevant positive sub-groups

- <25% PD-L1 is considered low/negative
- <1% PD-L1 is considered negative

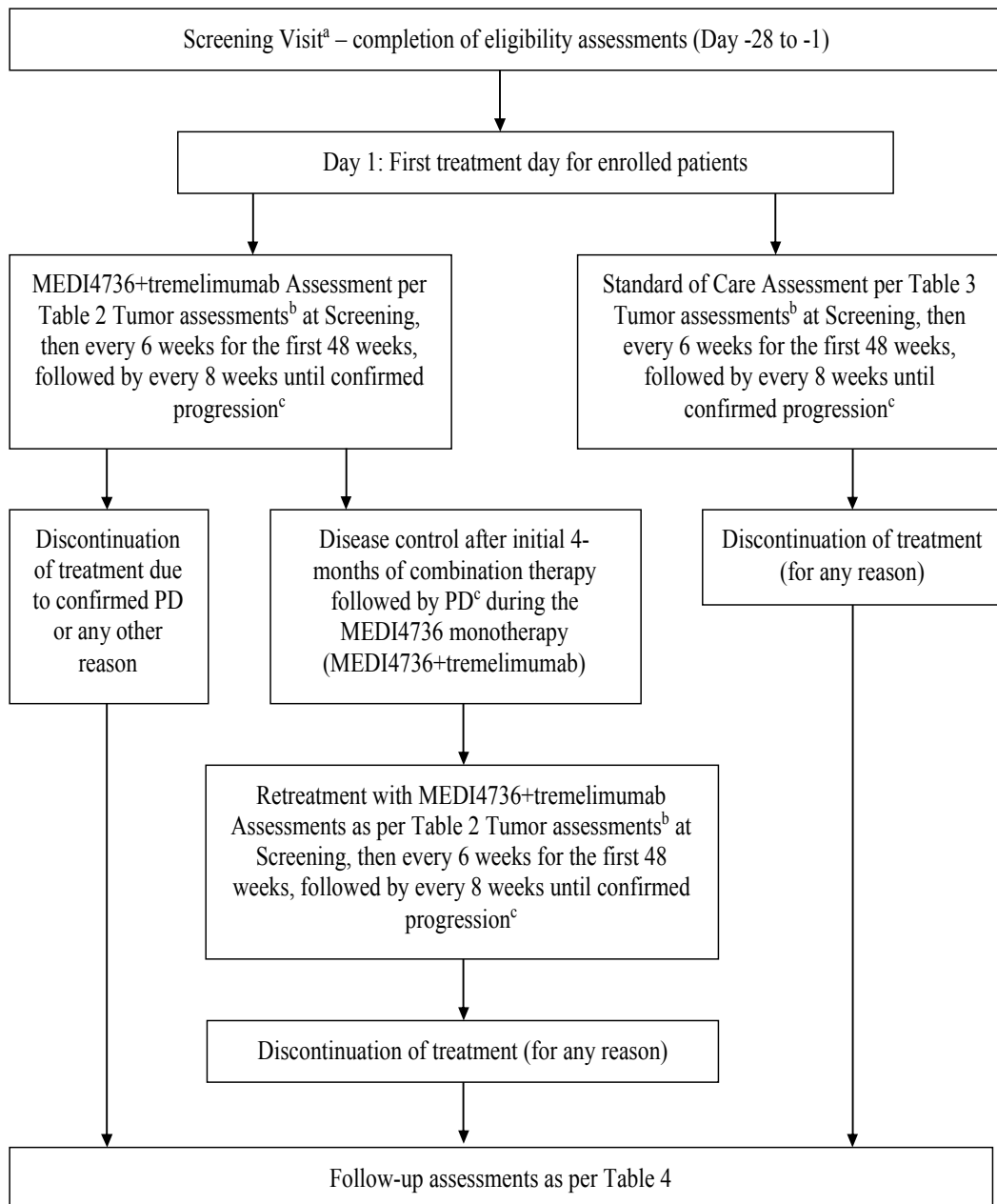
Patients will be randomized in a 1:1 ratio in a stratified manner according to PD-L1 tumor expression status ( $\geq 25\%$  versus  $< 25\%$ ), histology (squamous versus non-squamous), and smoking status (never smoker versus ever smoker) to receive treatment with MEDI4736 + tremelimumab combination therapy or SoC therapy. Doses and treatment regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 2, Table 3, and Table 4.

**Figure 1 Overall study design <sup>a</sup>**



- <sup>a</sup> The same study design will be applied to the China cohort. The number of patients in Figure 1 reflects those for the global cohort. Enrollment in China will continue after the global cohort enrollment is completed
- <sup>b</sup> Offer of standard chemotherapy per Investigator’s discretion
- <sup>c</sup> SoC is an Investigator choice from the following: paclitaxel + carboplatin, gemcitabine + cisplatin (or carboplatin) (squamous only), pemetrexed + cisplatin (or carboplatin) (non-squamous only), and for eligible patients, pemetrexed maintenance (non-squamous only following pemetrexed/platinum induction)

**Figure 2 Study flow chart**



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

<sup>b</sup> Tumor assessments were performed using RECIST 1.1

<sup>c</sup> A confirmatory scan is always required following the initial demonstration of PD (See Section 5.1 for more information)

## 2. STUDY OBJECTIVES

All objectives will be evaluated for all patients, unless otherwise indicated. The primary objective is assessment of overall survival (OS) in patients with bTMB  $\geq$  20mut/Mb.

### 2.1 Primary objective

| Primary objectives:   | Outcome measures: |
|---|-------------------|
| To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS in patients with bTMB $\geq$ 20mut/Mb. | OS                |

### 2.2 Secondary objectives

| Secondary objectives:  | Outcome measures:  |
|--|--|
| To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS   | OS in patients with <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 16mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 12 mut/Mb NSCLC</li> <li>• PD-L1-negative NSCLC</li> <li>• All patients with NSCLC</li> <li>• bTMB &lt; 20 mut/Mb NSCLC</li> <li>• bTMB non-evaluable population</li> </ul>   |
| To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS, ORR, DoR, OS12, OS18, OS24, APF12, and PFS2 | PFS, ORR, DoR and APF12 using Investigator assessments according to RECIST 1.1 in patients with <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 20mut/Mb NSCLC,</li> <li>• bTMB <math>\geq</math> 16mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 12mut/Mb NSCLC</li> <li>• PD-L1 negative NSCLC</li> <li>• All patients with NSCLC</li> </ul> PFS2 using local standard clinical practice <sup>a</sup> , OS12, OS18 and OS24 in patients with <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 20mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 16mut/Mb NSCLC</li> <li>• bTMB <math>\geq</math> 12mut/Mb NSCLC</li> <li>• PD-L1 negative NSCLC</li> <li>• All patients with NSCLC</li> </ul> |

| <b>Secondary objectives:</b>  | <b>Outcome measures:</b>  |
|---|---|
| To assess efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of ORR, PFS and OS in further PD-L1 defined populations    | OS in patients with PD-L1 TC $\geq$ 25% and PD-L1 TC $\geq$ 50%<br><br>PFS and ORR using Investigator assessments according to RECIST 1.1 in patients with PD-L1 TC $\geq$ 25% and PD-L1 TC $\geq$ 50%. |
| To further assess efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of ORR, PFS and OS (including OS12, OS18 and OS24) | OS in patients in analysis sets defined by tTMB cutoffs.<br><br>PFS and ORR using Investigator assessments according to RECIST 1.1 in patients in analysis sets defined by tTMB cutoffs <sup>b</sup> .  |
| To assess the pharmacokinetics (PK) of MEDI4736 + tremelimumab combination therapy  | Concentration of MEDI4736 and tremelimumab in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling)   |
| To investigate the immunogenicity of MEDI4736 and tremelimumab  | Presence of anti-drug antibodies (ADAs) for MEDI4736 and tremelimumab (confirmatory results: positive and negative; titers)   |

<sup>a</sup> PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint, or death

<sup>b</sup> tTMB cutoffs will be defined in the SAP ahead of the DBL from a dataset independent of data collected in this study.

### 2.3 Safety objective

| <b>Safety objective:</b>  | <b>Outcome measures:</b>   |
|---|--|
| To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy compared to SoC in the first-line setting for treatment of advanced or metastatic NSCLC patients | AEs, physical examinations, laboratory findings, and vital signs |



## 2.4 Exploratory objectives

| Exploratory objectives:   | Outcome measures:   |
|---|---|
| To investigate the relationship between PK exposure and clinical outcomes, efficacy, AEs, exploratory biomarkers, and/or safety parameters, if deemed appropriate   | A graphical and/or a data modeling approach will be used to analyze PK exposure and the relationship with clinical outcomes, efficacy, AEs, exploratory biomarkers, and/or safety parameters, as deemed appropriate   |
| To explore potential biomarkers in residual biological samples (eg, tumor and blood) including but not limited to, somatic mutations and gene expression in tumor and blood samples, which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to derive increased benefit to durvalumab + tremelimumab combination therapy | Correlation of candidate biomarkers with response/efficacy to durvalumab + tremelimumab combination therapy   |
| To investigate the relationship between a patient's PD-L1 expression levels in the tumor micro-environment and efficacy outcomes with durvalumab + tremelimumab, and SoC  | Tumoral and/or infiltrating IC expression of PD-L1 relative to efficacy outcomes (APF12, PFS, and OS)   |
| To investigate the relationship between a patient's tumor mutational burden (TMB) measured in tumor and/or blood and efficacy outcomes with durvalumab + tremelimumab, and SoC  | Correlation of bTMB and tTMB  |
| To investigate the relationship between biomarkers and clinical outcomes, efficacy, AEs, and/or safety parameters.  | OS, PFS, ORR, DoR and related outcome measures, e.g. OS12 will be assessed in subgroups defined by additional biomarkers e.g. tumor mutation burden and/or interferon-gamma signature assessed in tumor biopsies or gene expression in blood or circulating tumor DNA<br><br>A graphical and/or a data modeling approach will be used to analyze additional biomarkers and the relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate. |
| To explore the impact of subsequent anticancer therapies on OS  | An unbiased estimate of the comparison of OS between MEDI4736 + tremelimumab combination therapy and SoC in context of patients' subsequent therapies (e.g., patients from the SoC group who receive subsequent immuno-oncology treatments)   |

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

China patients will not undergo bTMB testing and analysis. Details of the China analysis will be outlined in detail in the China specific SAP. A further objective to meet China health authority requirement is to evaluate consistency in efficacy and safety among Chinese patients for benefit-risk assessment of MEDI4736 + tremelimumab combination therapy compared to SoC.

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

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

#### **3.1 Inclusion criteria**

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

1. Age  $\geq$ 18 years at the time of screening.
2. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. (For patients aged <20 years and enrolling in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative).
3. Histologically or cytologically documented Stage IV NSCLC not amendable to curative surgery or radiation (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology; [IASLC Staging Manual in Thoracic Oncology](#)).
4. Patients must have tumors that lack sensitizing EGFR mutation (e.g., exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) and ALK rearrangement. (If a patient has squamous histology or is known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required).
5. No prior chemotherapy or any other systemic therapy for advanced or metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for advanced disease are eligible, provided that progression has occurred >6 months from last therapy.
6. Tumor PD-L1 status, confirmed by a reference laboratory using the **CCI** [REDACTED], must be known prior to randomization. As such, all patients must be able to undergo a fresh tumor biopsy during screening or to provide an available

tumor sample taken <3 months prior to enrollment. Tumor lesions used for fresh biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. Fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component. The tumor specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC and other exploratory biomarker analysis and is preferred in formalin-fixed paraffin embedded blocks.

7. WHO/ ECOG performance status of 0 or 1 at enrollment.
8. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as  $\geq 10$  mm in the longest diameter (except lymph nodes which must have a short axis  $\geq 15$  mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.
9. No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.
10. Adequate organ and marrow function as defined below:
  - Hemoglobin  $\geq 9.0$  g/dL
  - Absolute neutrophil count  $\geq 1.5 \times 10^9$  /L
  - Platelet count  $\geq 100 \times 10^9$  /L
  - Serum bilirubin  $\leq 1.5 \times$  the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 2.5 \times$  ULN; for patients with hepatic metastases, ALT and AST  $\leq 5 \times$  ULN
  - Calculated creatinine clearance (CL)  $\geq 50$  mL/min as determined by Cockcroft-Gault (using actual body weight) or 24 hour urine collection

Males:

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

Females:

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

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

### **3.2 Exclusion criteria**

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

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.
3. Mixed small-cell lung cancer and NSCLC histology, sarcomatoid variant.
4. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
5. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of IP. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable.
6. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
7. History of allogenic organ transplantation.

8. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]) The following are exceptions to this criterion:
  - Patients with vitiligo or alopecia
  - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment
  - Any chronic skin condition that does not require systemic therapy
  - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
  - Patients with celiac disease controlled by diet alone
9. Uncontrolled intercurrent illness, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhea or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
10. Medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy.
11. History of another primary malignancy except for
  - Malignancy treated with curative intent and with no known active disease  $\geq 5$  years before the first dose of IP 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 (e.g., cervical cancer in situ)
12. History of leptomeningeal carcinomatosis.
13. Brain metastases or spinal cord compression unless the patient is stable (asymptomatic; no evidence of new or emerging brain metastases) and off steroids for at least 14 days prior to start of study treatment. Following radiotherapy and / or

surgery, patients with brain metastases must wait 4 weeks following the intervention and must confirm stability with imaging before randomization. Patients with suspected brain metastases at screening should have a CT/MRI of the brain prior to study entry.

14. History of active primary immunodeficiency
15. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16. Current or prior use of immunosuppressive medication within 14 days before the first dose of MEDI4736 or tremelimumab. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., 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 (e.g., CT scan premedication)
17. Receipt of live, attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.
18. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy.
19. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
20. Prior randomization or treatment in a previous MEDI4736 and/or tremelimumab clinical study regardless of treatment arm assignment.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section [3.4](#).

### 3.3 Patient enrollment and randomization

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

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

1. Obtain signed informed consent before any study specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization. For patients with a single target lesion, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approx. 2 weeks before imaging scans are acquired. (Informed consent of study procedures may be obtained prior to the 28 day screening window in order to permit tumor biopsy sample acquisition which must be analyzed prior to randomization).
2. Obtain a unique 7-digit enrollment number (E-code), through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
3. Obtain tumor sample and send for centralized PD-L1 testing. (Obtaining the tumor biopsy sample should be given the highest priority and, as such, the sample may be obtained and sent for PD-L1 expression status evaluation prior to the 28-day screening window (after obtaining signed informed consent) in order to permit analysis prior to randomization). The sample should be sent only for the patient with known EGFR and ALK status (if a patient has squamous histology or is known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required).  
  
If EGFR and ALK status is unknown, then the tumor sample (archive or fresh, primary or metastatic) should also be used to test for (local or central) EGFR mutation and ALK rearrangement in accordance with inclusion criteria 4.
4. Determine patient eligibility (see Sections 3.1 and 3.2).

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

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

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

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

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

If the patient is ineligible and not randomized, the IVRS/IWRS should be contacted to terminate the patient in the system.

Patients will begin treatment on Day 1. Patients must not be randomized and treated unless all eligibility criteria have been met.

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

### **3.4 Procedures for handling incorrectly enrolled patients**

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

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

### **3.5 Methods for assigning treatment groups**

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

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

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



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

### **3.6 Methods for ensuring blinding**

Not applicable; this study is not blinded.

### **3.7 Methods for unblinding**

Not applicable; this study is not blinded.

### **3.8 Restrictions**

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

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

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

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

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

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

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

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

| Barrier/Intrauterine methods  | Hormonal methods   |
|---|--|
| <ul style="list-style-type: none"> <li>• Copper T intrauterine device</li> <li>• Levonorgestrel-releasing intrauterine system (e.g., Mirena<sup>®</sup>)<sup>a</sup></li> </ul> | <ul style="list-style-type: none"> <li>• Implants: Etonogestrel-releasing implants: e.g. Implanon<sup>®</sup> or Norplan<sup>®</sup></li> <li>• Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing<sup>®</sup></li> <li>• Injection: Medroxyprogesterone injection: e.g. Depo-Provera<sup>®</sup></li> <li>• Combined Pill: Normal and low dose combined oral contraceptive pill</li> <li>• Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra<sup>®</sup></li> <li>• Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette<sup>®</sup> is currently the only highly effective progesterone based pill</li> </ul> |

<sup>a</sup> This is also considered a hormonal method

3. All patients: Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of MEDI4736 + tremelimumab combination therapy or 90 days after receipt of the final dose of MEDI4736 or until alternate anti-cancer therapy is started.
4. Restrictions relating to concomitant medications are described in Section 7.7.

### 3.9 Discontinuation of investigational product

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

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 3.10.2)
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (please see Section 6.10) or as defined in the local prescribing information for the SoC agent

- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (e.g., refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with IP

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

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

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see Table 4). All patients will be followed for survival until the end of the study. Patients who decline to return to the site for evaluations should be contacted by telephone as an alternative.

Patients who permanently discontinue study drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed q6w  $\pm$  1w for the first 48 weeks (relative to the date of randomization), and then q8w  $\pm$  1w thereafter until confirmed objective disease progression/death (whichever comes first) as defined in Table 2 and Table 4. For patients who permanently completed/discontinued treatment AND have had confirmed radiologic progression, additional scans are to be completed per standard practice post-progression (PFS2 follow-up).

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

## **3.10 Criteria for withdrawal of the patient from the study**

### **3.10.1 Screen failures**

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

### **3.10.2 Withdrawal of the informed consent**

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

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up (e.g., survival contact telephone calls)
- Withdrawal to the use of any samples (see Section 5.5.6)

#### **3.10.2.1 Survival status for withdrawn consent and lost to follow up patients**

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 9.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document all the attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is reestablished, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

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

- Lost to Follow up – site personnel should check hospital records, the patients’ current physician, and a publicly available death registry (if available) to obtain a current survival status in the 7 days following data cut-off. (The applicable CRF modules will be updated)
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status in the 7 days following data cutoff. (The applicable CRF modules will be updated).

### **3.11 Discontinuation of the study**

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

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

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

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

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

In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the patients’ interests. If this study is discontinued, all other studies involving MEDI4736 or tremelimumab will remain open to enrollment and screening, if deemed appropriate by AstraZeneca.

## **4. STUDY PLAN AND TIMING OF PROCEDURES**

The procedures for the screening and treatment periods in this study are presented in [Table 2](#) and [Table 3](#), and the procedures for the follow-up period are presented in [Table 4](#).

**For all treatment arms**

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

**For MEDI4736 + tremelimumab combination arms**

- Patients may delay dosing under certain circumstances
  - Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-mediated AE
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of MEDI4736 and tremelimumab (see current Investigator Brochures for MEDI4736 and tremelimumab)

**Standard of Care Arm:**

- Patients may delay and subsequently resume dosing per local standard clinical practice
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible

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

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



|   | Screening      | C1  | C2 | C3 | C4             | C5  | C6  | C7             | C8 to C12               | C13 <sup>a</sup><br>etc | For<br>details<br>see<br>Section |
|---|----------------|---|----|----|----------------|-----|-----|----------------|-------------------------|-------------------------|----------------------------------|
| <b>Week</b>   | -4 to -1       | 0   | 4  | 8  | 12             | 16  | 20  | 24             | 28, 32, 36, 40, 44      | 48 etc                  |                                  |
| <b>Day</b>  | -28 to -1      | 1   | 29 | 57 | 85             | 113 | 141 | 169            | 197, 225, 253, 281, 309 | 337 etc                 |                                  |
| <b>Window (days)</b>  | NA             | +3 <sup>b</sup>   | ±3 | ±3 | ±3             | ±3  | ±3  | ±3             | ±3                      | ±3                      |                                  |
| <b>Pharmacokinetics</b>   |                |   |    |    |                |     |     |                |                         |                         |                                  |
| MEDI4736 PK sample (serum)  |                | X <sup>i</sup>  |    |    | X <sup>i</sup> |     |     | X <sup>j</sup> |                         |                         | 5.4.1                            |
| Tremelimumab PK sample (serum; combination therapy group only)                            |                | X <sup>i</sup>  |    |    | X <sup>i</sup> |     |     |                |                         |                         | 5.4.1                            |
| <b>Monitoring</b>   |                |   |    |    |                |     |     |                |                         |                         |                                  |
| WHO/ECOG performance status   | X              | X   | X  | X  | X              | X   | X   | X              | X                       | X                       | 5.3.1                            |
| AE/SAE assessment   | <----->        |   |    |    |                |     |     |                |                         |                         | 6.3.1                            |
| Drug accountability   |                | X   | X  | X  | X              | X   | X   | X              | X                       | X                       | 7.6                              |
| <b>Pre-randomization medication</b>   |                |   |    |    |                |     |     |                |                         |                         |                                  |
| Folic acid <sup>k</sup>   | X              | Discontinue as randomized to combination therapy  |    |    |                |     |     |                |                         |                         | 3.3                              |
| IM Vitamin B12 <sup>k</sup>   | X              | Discontinue as randomized to combination therapy  |    |    |                |     |     |                |                         |                         | 3.3                              |
| <b>IP administration</b>  |                |   |    |    |                |     |     |                |                         |                         |                                  |
| MEDI4736 (combination therapy) <sup>l,m</sup>   |                | X   | X  | X  | X              | X   | X   | X              | X                       | X                       | 7.2.1                            |
| Tremelimumab <sup>l,m</sup>   |                | X   | X  | X  | X              |     |     |                |                         |                         | 7.2.1                            |
| <b>Other laboratory assessments and assays</b>  |                |   |    |    |                |     |     |                |                         |                         |                                  |
| Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation) |                | X   |    |    | X              |     |     | X <sup>r</sup> |                         |                         | 5.4.2                            |
| Tumor biopsy (newly acquired or archived <3 months old)                                   | X <sup>c</sup> |   |    |    |                |     |     |                |                         |                         | 5.5.1                            |
| Archival tumor sample ≥3 months old, if available <sup>n</sup>                            | X              |   |    |    |                |     |     |                |                         |                         | 5.5.1                            |
| EGFR and ALK test   | X <sup>o</sup> |   |    |    |                |     |     |                |                         |                         | 3.3                              |
| Tumor evaluation (CT or MRI) (RECIST 1.1) <sup>p,q</sup>                                  | X              | q6w±1w for the first 48 weeks relative to the date of randomization, and then q8w±1w thereafter |    |    |                |     |     |                |                         |                         | 5.1                              |

- a Patients who continue on treatment will be assessed in the same manner
- b Every effort should be made to minimize the time between randomization and starting treatment. (i.e. on the same day after randomization)
- c Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. The collection of tumor biopsies at the time of progression prior to retreatment is mandated; the Investigator must consult with the Study Physician if such sampling is not feasible. The collection of additional biopsies upon progression is strongly encouraged
- d Body weight is recorded along with vital signs
- e Any clinically significant abnormalities detected require a confirmatory ECG
- f If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1
- g Except screening visit, free T<sub>3</sub> and free T<sub>4</sub> will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
- h For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion
- i Pre-dose same day as infusion and within 1 hour of end of infusion
- j Pre-dose only
- k To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed if randomized to SoC group
- l During the combination portion of treatment, tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion. If there are no clinically significant infusion reactions with the first cycle, then for all other cycles, the MEDI4736 can be given immediately after the tremelimumab infusion has finished
- m Results for urea and electrolytes, full blood count, and LFTs must be available before commencing an infusion (within 3 days)
- n Not collected in China
- o For patients with unknown status of ALK and/or EGFR NSCLC (if patients have squamous histology or are known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required)
- p RECIST 1.1 assessments will be performed on CT/MRI images of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible and prior to the start of IP. The radiological progression confirmatory scans should be performed no less than 4 weeks after the prior assessment of PD and preferably at the next scheduled visit (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit
- q Patients with confirmed PD can continue to receive MEDI4736 + tremelimumab combination therapy at the discretion of the Investigator
- r MEDI4736 sample only at this time point

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

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

Note: “Retreatment” is not permitted after the completion of final analysis for the respective patient.

ADA Anti-drug antibody; AE Adverse event; ALK Anaplastic lymphoma kinase; APTT activated partial thromboplastin time; C Cycle; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; HIV Human immunodeficiency virus; IM Intramuscular; IP Investigational product; INR international normalized ratio; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; PD Progressive disease;; ; PK Pharmacokinetic(s); RNA Ribonucleic acid; SAE Serious adverse event; q6w Every 6 weeks; q8w Every 8 weeks; SNP Single nucleotide polymorphism; T<sub>3</sub> Triiodothyronine; T<sub>4</sub> Thyroxine; TSH Thyroid-stimulating hormone; w Week; WHO World Health Organization

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

|   | Screening      | C1                      | C2 | C3 | C4 | C5 | C6  | C7  | C8  | C9  | C10 to C17                             | C18, C19, etc | For details see Section |
|---|----------------|-------------------------|----|----|----|----|-----|-----|-----|-----|--|---------------|-------------------------|
| <b>Week</b>   | -4 to -1       | 0                       | 3  | 6  | 9  | 12 | 15  | 18  | 21  | 24  | 27, 30, 33, 36, 39, 42, 45, 48         | 51, 54, etc   |                         |
| <b>Day</b>  | -28 to -1      | 1                       | 22 | 43 | 64 | 85 | 106 | 127 | 148 | 169 | 190, 211, 232, 253, 274, 295, 316, 337 | 358, 379, etc |                         |
| <b>Window (days)</b>  | NA             | +3 <sup>a</sup>         | ±3 | ±3 | ±3 | ±3 | ±3  | ±3  | ±3  | ±3  | ±3                                     | ±3            |                         |
| <b>Informed consent</b>   |                |                         |    |    |    |    |     |     |     |     |  |               |                         |
| Informed consent: study procedures                              | X <sup>b</sup> |                         |    |    |    |    |     |     |     |     |  |               | 4.1, 10.4               |
| <b>Study procedures</b>   |                |                         |    |    |    |    |     |     |     |     |  |               |                         |
| Physical exam (full)  | X              |                         |    |    |    |    |     |     |     |     |  |               | 5.2.2                   |
| Targeted physical exam (based on symptoms)                      |                | X                       | X  | X  | X  | X  | X   | X   | X   | X   | X                                      | X             | 5.2.2                   |
| Vital signs <sup>c</sup>  | X              | X                       | X  | X  | X  | X  | X   | X   | X   | X   | X                                      | X             | 5.2.4                   |
| ECG <sup>d</sup>  | X              | As clinically indicated |    |    |    |    |     |     |     |     |  |               | 5.2.3                   |
| Concomitant medications   | ←-----→        |                         |    |    |    |    |     |     |     |     |  |               | 7.7                     |
| Demography, including baseline characteristics and tobacco use  | X              |                         |    |    |    |    |     |     |     |     |  |               | 4.1                     |
| Eligibility criteria  | X              |                         |    |    |    |    |     |     |     |     |  |               | 3.1, 3.2                |
| <b>Laboratory assessments</b>                                   |                |                         |    |    |    |    |     |     |     |     |  |               |                         |
| Clinical chemistry <sup>e,f</sup>                               | X              | X                       | X  | X  | X  | X  | X   | X   | X   | X   | X                                      | X             | Table 5                 |
| Hematology <sup>e,f</sup>                                       | X              | X                       | X  | X  | X  | X  | X   | X   | X   | X   | X                                      | X             | Table 6                 |
| APTT and INR  | ←-----→        |                         |    |    |    |    |     |     |     |     |  |               |                         |
| TSH, free T <sub>3</sub> , and free T <sub>4</sub> <sup>g</sup> | X              |                         |    |    |    | X  |     |     |     | X   |  |               | 5.2.1                   |
| Urinalysis  | X              |                         |    |    |    |    |     |     |     |     |  |               | Table 7                 |
| Hepatitis B and C and HIV                                       | X              |                         |    |    |    |    |     |     |     |     |  |               | 5.2.1                   |
| Pregnancy test <sup>h</sup>                                     | X              | As clinically indicated |    |    |    |    |     |     |     |     |  |               | 5.2.1                   |

|   | Screening      | C1  | C2        | C3 | C4 | C5 | C6  | C7  | C8  | C9  | C10 to C17                             | C18, C19, etc | For details see Section |
|---|----------------|---|-----------|----|----|----|-----|-----|-----|-----|--|---------------|-------------------------|
| <b>Week</b>   | -4 to -1       | 0   | 3         | 6  | 9  | 12 | 15  | 18  | 21  | 24  | 27, 30, 33, 36, 39, 42, 45, 48         | 51, 54, etc   |                         |
| <b>Day</b>  | -28 to -1      | 1   | 22        | 43 | 64 | 85 | 106 | 127 | 148 | 169 | 190, 211, 232, 253, 274, 295, 316, 337 | 358, 379, etc |                         |
| <b>Window (days)</b>  | NA             | +3 <sup>a</sup>   | ±3        | ±3 | ±3 | ±3 | ±3  | ±3  | ±3  | ±3  | ±3                                     | ±3            |                         |
| <b>Monitoring</b>   |                |   |           |    |    |    |     |     |     |     |  |               |                         |
| WHO/ECOG performance status                                     | X              | X   | X         | X  | X  | X  | X   | X   | X   | X   | X                                      | X             | 5.3.1                   |
| AE/SAE assessment   | <----->        |   |           |    |    |    |     |     |     |     |  |               | 6.3.1                   |
| <b>Pre-randomization medication</b>                             |                |   |           |    |    |    |     |     |     |     |  |               |                         |
| Folic acid <sup>i</sup>   | X              | Continue in line with local practice  |           |    |    |    |     |     |     |     |  | 3.3           |                         |
| IM Vitamin B12 <sup>i</sup>                                     | X              | Continue in line with local practice  |           |    |    |    |     |     |     |     |  | 3.3           |                         |
| <b>SoC administration</b>                                       |                |   |           |    |    |    |     |     |     |     |  |               |                         |
| Platinum-based chemotherapy                                     |                | X   | Cycle q3w |    |    |    |     |     |     |     |  | 7.2.1         |                         |
| <b>Other laboratory assessments and assays</b>                  |                |   |           |    |    |    |     |     |     |     |  |               |                         |
| Tumor biopsy (newly acquired or archived <3 months old)         | X <sup>b</sup> |   |           |    |    |    |     |     |     |     |  |               | 5.5.1                   |
| Archival tumor sample ≥ 3 months old, if available <sup>k</sup> | X              |   |           |    |    |    |     |     |     |     |  |               | 5.5.1                   |
| EGFR and ALK test   | X <sup>j</sup> |   |           |    |    |    |     |     |     |     |  |               | 3.3                     |
| Tumor evaluation (CT or MRI) (RECIST 1.1) <sup>l</sup>          | X              | q6w ± 1w for the first 48 weeks relative to the date of randomization, and then q8w±1w thereafter |           |    |    |    |     |     |     |     |  | 5.1           |                         |

<sup>a</sup> Every effort should be made to minimize the time between randomization and starting treatment. (ie. on the same day after randomization)  
<sup>b</sup> Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization  
<sup>c</sup> Before every infusion or administration and as clinically indicated. Body weight is included in vital signs  
<sup>d</sup> Any clinically significant abnormalities detected require a confirmatory ECG  
<sup>e</sup> To be collected q3w prior to the start of infusion and as clinically indicated  
<sup>f</sup> If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1  
<sup>g</sup> Free T<sub>3</sub> and free T<sub>4</sub> will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system  
<sup>h</sup> For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

- i To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed if randomized to SoC group
- j For patients with unknown status of ALK and/or EGFR NSCLC (if patients have squamous histology or are known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required)
- k Not collected in China
- l RECIST 1.1 assessments will be performed on CT/MRI images of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible and prior to the start of IP. The radiological progression confirmatory scans should be performed no less than 4 weeks after the prior assessment of PD and preferably at the next scheduled visit (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit

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

ADA Anti-drug antibody; AE Adverse event; ALK Anaplastic lymphoma kinase; APTT activated partial thromboplastin time; C Cycle; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; HIV Human immunodeficiency virus; IM Intramuscular; INR international normalized ratio; IP Investigational product; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; q6w Every 6 weeks; q8w Every 8 weeks; PD Progressive disease; PK Pharmacokinetic(s); RNA Ribonucleic acid; SAE Serious adverse event; SNP Single nucleotide polymorphism; T<sub>3</sub> Triiodothyronine; T<sub>4</sub> Thyroxine; TSH Thyroid-stimulating hormone; w Week; WHO World Health Organization

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

| Evaluation   | Time since last dose of IP  |                         |   |   |   |   |    |   | For details see Section |
|--|---|-------------------------|---|---|---|---|----|---|-------------------------|
|  | Day ( $\pm 3$ )   | Months ( $\pm 1$ week)  |   |   |   |   |    | 12 months and every 2 months ( $\pm 2$ weeks) |                         |
|  | 30  | 2                       | 3 | 4 | 6 | 8 | 10 |   |                         |
| Physical examination (full) <sup>a</sup>   | X   |                         |   |   |   |   |    |   | 5.2.2                   |
| Vital signs (temperature, respiratory rate, blood pressure, and pulse)                                 | X   |                         |   |   |   |   |    |   | 5.2.4                   |
| Weight   | X   | X                       | X |   | X |   |    |   | 5.2.4                   |
| Pregnancy test <sup>b</sup>  | X   | As clinically indicated |   |   |   |   |    |   | 5.2.1                   |
| AE/SAE assessment <sup>c</sup>   | X   | X                       | X |   |   |   |    |   | 6.3.1                   |
| Concomitant medications  | X   | X                       | X |   |   |   |    |   | 7.7                     |
| WHO/ECOG performance status  | At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy <sup>d</sup>   |                         |   |   |   |   |    |   | 5.3.1                   |
| Subsequent anticancer therapy <sup>e</sup> ; and second progression assessment <sup>f,g</sup>          | ←----->   |                         |   |   |   |   |    |   | NA                      |
| Survival status <sup>h</sup>   |   | X                       | X | X | X | X | X  | X   | 5.1                     |
| Hematology   | X   | X                       | X |   |   |   |    |   | Table 6                 |
| Clinical chemistry   | X   | X                       | X |   |   |   |    |   | Table 5                 |
| TSH, free T <sub>3</sub> , and free T <sub>4</sub> <sup>i</sup>  | X   |                         |   |   |   |   |    |   | 5.2.1                   |
| PK assessment <sup>j</sup>   |   |                         | X |   |   |   |    |   | 5.4.1                   |
| Immunogenicity assessment (ADA sampling) to identify ADA responses in patient circulation <sup>l</sup> |   |                         | X |   | X |   |    |   | 5.4.2                   |
| Tumor assessment (CT or MRI) <sup>k</sup>  | q6w $\pm$ 1w for the first 48 weeks (relative to the date of randomization), and then q8w $\pm$ 1w thereafter until confirmed objective disease progression/death (whichever comes first). Additional scans to be completed per standard practice post-progression. |                         |   |   |   |   |    |   | 5.1                     |

<sup>a</sup> Physical exams are described in Section 5.2.2

<sup>b</sup> For women of childbearing potential only. A urine or serum pregnancy test is acceptable

<sup>c</sup> The AE/SAE follow-up for SoC is only 30 days

- <sup>d</sup> WHO/ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible
- <sup>e</sup> Details of any treatment for NSCLC (including surgery) post the last dose of IP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy
- <sup>f</sup> PFS2 assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death
- <sup>g</sup> For patients who discontinue their assigned IP following confirmed progression, available readings of CT/MRI from local practice will be collected from patients' medical charts while information on subsequent anticancer treatment and/or PFS2 is collected
- <sup>h</sup> Patients may be contacted in the week following data cut-offs to confirm survival status. Details of any treatment for NSCLC (including surgery) post the last dose of IP must be recorded in the eCRF
- <sup>i</sup> Free T<sub>3</sub> and free T<sub>4</sub> will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system
- <sup>j</sup> For patients in the MEDI4736 + tremelimumab combination therapy group only. The follow-up samples (3 and 6 months) for each molecule is relative to the respective last dose
- <sup>k</sup> Only for patients yet to progress, RECIST 1.1 assessments will be performed using CT/MRI assessments of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients. The confirmatory scans should preferably be performed no less than 4 weeks after the initial assessment of PD and preferably at the next scheduled visit (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database

ADA Anti-drug antibody; AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; eCRF electronic case report form; IP Investigational product; MRI Magnetic resonance imaging; NA Not applicable; NSCLC Non-small-cell lung cancer; PD Progressive disease; q6w Every 6 weeks; q8w Every 8 weeks; RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; T<sub>3</sub> Triiodothyronine; T<sub>4</sub> Thyroxine; TSH Thyroid-stimulating hormone; w Week; WHO World Health Organization

## **4.1 Enrollment/screening period**

All screening and enrollment procedures will be performed according to the assessment schedule in [Table 2](#) and [Table 3](#). Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must be obtained within 28 days of randomization. All patients will be required to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient informed consent form (ICF).

Screening evaluations may be performed over more than 1 visit.

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

## **4.2 Treatment period**

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

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

## **4.3 Follow-up period**

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see [Table 4](#)).

Whenever vital signs, electrocardiograms (ECGs), and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the timepoints indicated in [Table 4](#).



## 5. STUDY ASSESSMENTS

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

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

### 5.1 Efficacy assessments

This study will evaluate the primary endpoint of OS. In addition, RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS, ORR, DoR, and APF12 using Investigator assessments. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions and the objective tumor response criteria (CR, PR, SD, or PD) are presented in [Appendix D](#). PFS2 defined by local standard clinical practice will also be evaluated.

Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen including the entire liver and both adrenals, collected during screening/baseline and at regular (follow-up) intervals during study treatment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The RECIST 1.1 guidelines ([Appendix D](#)) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify target (defined measurable) and non-target lesions, and each lesion (and any new lesion) is evaluated in subsequent, on-treatment follow-up images. This allows determination of follow-up target lesion response, non-target lesion response, and overall time-point tumor responses (CR, PR, SD, PD or NE).

Efficacy for all patients (all cohorts) will be assessed on images collected q6w  $\pm$  1w for the first 48 weeks relative to the date of randomization, and q8w  $\pm$  1w thereafter until confirmed objective disease progression or off-study. It is important to follow the assessment schedule as closely as possible [refer to the study plans in [Table 2](#), and [Table 3](#) (screening and treatment period), and [Table 4](#) (follow up)]. If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her next regularly scheduled imaging visit.

According to RECIST 1.1 modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of progression, preferably at the next scheduled imaging visit and no earlier than 4 weeks after the previous assessment of PD in the

absence of clinically significant deterioration. Treatment will continue between the initial assessment of progression and confirmation for progression.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) after the initial assessment of progression, then the patient should continue to be followed with scheduled imaging until confirmed objective disease progression.

**Confirmation of progression guidelines are set for the following reasons:**

- For patient management and treatment decisions
- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudo-progression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression
- When scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (Investigator assesses PD at a time-point earlier than does BICR)

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration confirmed by a radiological scan if clinically feasible; or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- $\geq 20\%$  increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point)
- and/or additional new unequivocal lesions at the confirmatory scan time-point

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first PD by RECIST 1.1 is not confirmed, continue with

assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

Following confirmed progression, patients should continue to be followed-up for survival every 2 months (8 weeks) as outlined in the follow-up schedules of assessments (Table 4). In addition, all patients will be contacted in the week following data cutoff to confirm survival status.

Patients in the MEDI4736 + tremelimumab combination arm who complete 4 doses/dosing cycles (with clinical benefit per Investigator judgment) and subsequently have PD during treatment with MEDI4736 alone may restart combination treatment if they meet eligibility criteria for retreatment (see Section 7.2.2). Patients who restart treatment after PD must have a baseline tumor assessment within 28 days of restarting treatment with MEDI4736 + tremelimumab combination therapy; all further scans should occur q6w ( $\pm 7$  days) relative to the date of randomization until confirmed disease progression.

### 5.1.1 Central reading of scans

Blinded Independent Central Review assessments are not planned for this study. However, all images will be collected centrally so that the scans will be available if such verification becomes necessary. Guidelines for imaging collection and storage will be provided in a separate document. The management of patients will be based solely upon the results of the RECIST assessment conducted by the Investigator.

After data cut-off for the primary analysis of OS in the patients randomized prior to the end of global recruitment has been completed, no further central collection of scans is required except for sites in China. Any patients in China (either recruited prior to the end of the global recruitment or as part of the additional China cohort) should continue with central collection of until the cut-off date of China OS analysis.

### **5.1.2 Survival assessments**

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

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

## **5.2 Safety assessments**

### **5.2.1 Laboratory safety assessments**

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

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum  $\beta$ -hCG) samples will be performed for pre-menopausal women of childbearing potential at screening and subsequent visits as specified in the assessment schedule (see [Table 2](#), [Table 3](#), and [Table 4](#)). Tests will be performed by the hospital's local laboratory. If results are positive, the patient must not start or continue treatment. In the event of a suspected pregnancy during the study, the test should be repeated.

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

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

Other safety tests to be performed at screening include assessment for HBV surface antigen, HCV antibodies, HIV antibodies, thyroid-stimulating hormone, free triiodothyronine (T<sub>3</sub>), and free thyroxine (T<sub>4</sub>).

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

|  |  |
|--|--|
| Albumin                                | Lactate dehydrogenase                                    |
| Alkaline phosphatase                   | Lipase <sup>b</sup>                                      |
| ALT <sup>a</sup>                       | Magnesium <sup>c</sup>                                   |
| Amylase <sup>b</sup>                   | Potassium  |
| AST <sup>a</sup>                       | Sodium   |
| Bicarbonate <sup>c</sup>               | Total bilirubin <sup>b</sup>                             |
| Calcium                                | Total protein  |
| Chloride <sup>c</sup>                  | TSH  |
| Creatinine clearance <sup>c</sup>      | T3 free <sup>d</sup> (reflex)                            |
| Creatinine                             | T4 free <sup>d</sup> (reflex)                            |
| Gamma glutamyltransferase <sup>c</sup> | Urea or blood urea nitrogen, depending on local practice |
| Glucose                                |  |

a Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is  $\geq 2x$  upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

b It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable

c Bicarbonate (where available), Chloride, Creatinine clearance, gamma glutamyltransferase, magnesium, testing are to be performed at screening, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated

d Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid Stimulating Hormone

**Table 6 Hematology**

|   |   |
|---|---|
| Basophils                                 | Mean corpuscular volume   |
| Eosinophils                               | Monocytes   |
| Hematocrit                                | Neutrophils   |
| Hemoglobin                                | Platelet count  |
| Lymphocytes                               | Red blood cell count  |
| Mean corpuscular hemoglobin               | Total white cell count  |
| Mean corpuscular hemoglobin concentration | Activated partial thromboplastin time and international normalized ratio <sup>a</sup> |

<sup>a</sup> For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated

**Table 7 Urinalysis**

Urinalysis should be done at baseline (screening) and then as clinically indicated.

---

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

---

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

If a patient shows an AST or ALT  $\geq 3 \times$  ULN together with total bilirubin  $\geq 2 \times$  ULN, refer to [Appendix C](#) for further instructions. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days ( $\pm 3$  days), 2 months ( $\pm 1$  week) and 3 months ( $\pm 1$  week) after permanent discontinuation of IP.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section [6.1.4](#).

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

### **5.2.2 Physical examination**

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

### **5.2.3 Electrocardiograms**

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

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

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

#### **5.2.4 Vital signs**

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules (see [Table 2](#), [Table 3](#), and [Table 4](#)). Body weight is also recorded along with vital signs.

##### **First Infusion**

For the first infusion day, patients in the MEDI4736 + tremelimumab treatment group will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients in the MEDI4736 + tremelimumab combination therapy group before, during, and after each 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 [i.e., 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)

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. A 1-hour observation period is recommended after the first infusion of MEDI4736 and tremelimumab.

##### **Subsequent Infusion**

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

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

The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section [6.1.4](#). For any adverse events of infusion reactions please enter the vital signs values into the CRF.

## **5.3 Other assessments**

### **5.3.1 WHO/ECOG performance status**

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

0. Fully active; able to carry out all usual activities without restrictions.
1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (e.g., light housework or 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; unable to carry out any self-care and totally confined to bed or chair.
5. Dead

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

### **5.3.2 Other safety assessments**

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (please see [Section 6.10](#)) will be applied. The results of the full diagnostic workup including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters etc will be captured in a separate questionnaire. 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 pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

## **5.4 Pharmacokinetics**

### **5.4.1 Collection of samples and determination of drug concentration**

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

Samples for determination of MEDI4736 and tremelimumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.



#### **5.4.2 Collection of samples to measure for the presence of ADAs**

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

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for both IPs (MEDI4736 and tremelimumab) 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.

#### **5.4.3 Storage and destruction of pharmacokinetic/ADA samples**

PK and ADA samples will be disposed of a maximum of 15 years after the study ends.

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analysis may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analysis may be reported separately from the Clinical Study Report (CSR).

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

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 AstraZeneca or its designated Biobank; see details in the Laboratory Manual).

PK and ADA samples collected in China will be destroyed after finalization of the bioanalytical reports.

### **5.5 Biomarker analysis**

The patient's consent to the use of donated biological samples is mandatory. Tissue samples will be obtained from all screened patients.

Pre-treatment bTMB and tTMB will be evaluated in all patients with available samples. Data will be compared between groups to determine if baseline TMB is prognostic and/or predictive of outcomes associated with MEDI4736 + tremelimumab combination therapy vs SoC.

The **CCI**, a next generation sequencing platform, will be used to assess the tumor mutational burden in circulating tumor DNA from blood samples at baseline. For tissue based tumor mutational burden (tTMB), the assessment will be performed by **CCI**.

Pre-treatment tumor PD-L1 expression will also be evaluated in all randomized patients. Data will be compared between groups to determine if baseline PD-L1 expression is prognostic

and/or predictive of outcomes associated with MEDI4736 + tremelimumab combination therapy versus SoC. Baseline tumor requirements are briefly described in Section 5.5.1.

Based on availability of tissue, additional exploratory biomarkers may be evaluated as described in Section 5.5.2. Also, descriptions of exploratory, peripheral measures are described in this section. Samples will be obtained according to the assessment schedules provided in Table 2, Table 3, and Table 4.

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

All samples collected for biomarker analysis will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy.

The results may be pooled with biomarker data from other MEDI4736/tremelimumab studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

### **5.5.1 Collection of patient samples for stratification by PD-L1 and for expression of PD-L1 and Tumor Mutation Burden (TMB)**

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

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

Samples should be collected via a core needle (18 gauge or larger) or be collected as an excisional or incisional tumor biopsy sample.

When tissue is newly obtained for the purpose of entry into this study, 2 cores should be placed in formalin and processed to a single paraffin embedded block, as described in the Laboratory Manual.

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

Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy. For patients with a single target lesion, if screening biopsy is collected prior to

screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired

- **MANDATORY:** The collection of additional archived tumor tissue block greater than 3 months old (formalin-fixed paraffin-embedded) is mandated, where such samples exist in a quantity sufficient to allow for analysis. Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. Please consult the laboratory manual for specific instructions and guidelines regarding sections. Sample not collected in China.
- **MANDATORY:** The collection of tumor biopsies at the time of progression prior to retreatment is mandated. The Investigator can consult with the Study Physician if such sampling is not feasible, but retreatment is indicated. Sample not collected in China.
- **OPTIONAL:** The collection of additional biopsies upon progression of patients in the MEDI4736 + tremelimumab combination therapy group is strongly encouraged. Also, the collection of biopsies upon progression for patients in the SoC group is optional. Not applicable in China.
- Additional tumor biopsies collected as part of clinical care (e.g., for mixed responses or upon PD) can be submitted for further analysis. Not applicable in China.

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

A brief description of exploratory tumor markers likely to be explored by IHC, DNA or ribonucleic acid (RNA) analysis is provided in Section 5.5.2.

Plasma sample collected at baseline for biomarker analysis will be used for assessment of blood TMB, on which the primary and secondary objectives are based.

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

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

### **Tumor Mutational Burden**

Tissue TMB will be assessed in tumor tissue using the CCI [REDACTED], where sufficient tumor sample is available. Blood TMB will be assessed in ctDNA from plasma, using the CCI [REDACTED]

Based on blood TMB or tissue TMB levels, OS, PFS ORR and other outcome variables will be evaluated for durvalumab + tremelimumab combination therapy versus SoC therapy in patients with high TMB levels and also with low TMB levels according to pre-specified and exploratory cut-off points.

Note: In China ctDNA samples will not be collected, nor will TMB be assayed in tumor samples.

### **5.5.2 Exploratory biomarkers**

Tumor samples for exploratory biomarker analysis will be obtained according to the schedules presented in [Table 2](#), [Table 3](#), and [Table 4](#) and section 5.5 and Laboratory manual. Details for collection, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

OS, PFS, ORR, DoR and related outcome measures, e.g. OS12 will be assessed in subgroups defined by additional biomarkers e.g. interferon-gamma signature assessed in tumor biopsies or gene expression in blood or circulating tumor DNA.

Note that samples will be obtained from patients randomized to each treatment group. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with MEDI4736 + tremelimumab combination therapy versus SoC therapies, subgrouped by histology.

Additional sample collections and analysis may be completed at select study sites by site-specific amendment. All samples collected for such exploratory analysis will be stored at site, a reference laboratory, or at AstraZeneca's facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.

### **Tumor markers**

Tissue obtained as part of screening procedures and for establishing PD-L1 expression status will be analyzed for additional markers by IHC. A primary goal is to measure cluster of differentiation (CD)8 and CD4/FoxP3 protein expression in an effort to enumerate cytotoxic versus regulatory T cells. Based on availability of tissue, a panel of additional, immune-relevant markers expressed on tumor-infiltrating lymphocytes or on tumour cells may be assessed. Markers of special interest include, but are not limited to, Ox40, GITR, PD-L2, Tim-3, CD137, and Lag 3.

Other tissue-based approaches may be pursued including RT-QPCR and in situ hybridization (e.g., for detection of IFN gamma signaling genes such as CXCL9, CXCL10, and IFN gamma itself), and/or somatic mutation detection methodologies.

IFN gamma is a critical driver of programmed death ligand-1 (PD-L1) expression in cancer and host cells, and baseline intratumoral T cell infiltration may improve response likelihood to anti-PD-1/PD-L1 therapies in NSCLC ([Higgs et al 2017](#)) and other settings ([Ayers et al](#)

2017). Therefore, baseline expression of IFN gamma signaling genes such as CXCL9, CXCL10, and IFN gamma itself are of interest as a biomarker of response to MEDI4736 + tremelimumab.

### **Management of biomarker data**

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

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

#### **5.5.3 Storage, re-use, and destruction of biological samples**

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analysis for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving MEDI4736 or tremelimumab to generate hypotheses to be tested in future research.

Tumour samples collected in China for PD-L1 testing will be destroyed or repatriated maximally 5 years after study drug is approved for marketing in China.

#### **5.5.4 Labeling and shipment of biological samples**

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see [Appendix B](#) "IATA 6.2 Guidance Document".

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

#### **5.5.5 Chain of custody of biological samples**

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of sample shipments.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of sample shipments.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobank and will be registered with the AstraZeneca Biobank Team during the entire life cycle.

This does not apply to samples collected in China.

### **5.5.6 Withdrawal of informed consent for donated biological samples**

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented
- Ensure that the laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented.
- Ensure that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action is documented and the study site is informed.

## **5.6 Pharmacogenetics (Not applicable)**

## **6. SAFETY REPORTING AND MEDICAL MANAGEMENT**

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

## **6.1 Definition of adverse events**

An AE is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition during or following exposure to a pharmaceutical product, whether or not the condition is considered to be causally related to the product. An undesirable medical condition can be a symptom (e.g., nausea or chest pain), sign (e.g., tachycardia or enlarged liver), or the abnormal result of an investigation (e.g., laboratory findings or ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no IP has been administered.

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

### **6.1.1 Causality collection**

The Investigator will assess the causal relationship between the IPs and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

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

A guide to the interpretation of the causality question is found in [Appendix A](#).

### **6.1.2 Relationship to protocol procedures**

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment-emergent (i.e., SAEs that occur prior to the administration of IP or SoC) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient’s medical record
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient’s medical record

### **6.1.3 Adverse events based on signs and symptoms**

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit/you were last asked?” or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a

list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

#### **6.1.4 Adverse events based on examinations and tests**

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IPs.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

#### **6.1.5 Hy's law**

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT  $\geq 3 \times$  ULN together with total bilirubin  $\geq 2 \times$  ULN may need to be reported as SAEs. Please refer to [Appendix C](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

#### **6.1.6 Disease progression**

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

#### **6.1.7 New cancers**

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.



### **6.1.8 Deaths**

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of IP, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should not be reported as an SAE
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Drug Safety or its representative within the usual timeframes

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug then it should also be reported as an SAE.

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

For patients continuing to receive MEDI4736/tremelimumab treatment after scheduled DCO for final analysis of the global cohort and database lock, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with MEDI4736/tremelimumab to manage AEs in accordance with the MEDI4736/tremelimumab toxicity management guidelines (please see Section 6.10). All data post the scheduled DCO for final analysis for global cohort and database lock will be managed as per one of the options listed in "Post Data Cut off" part of Section 7.2.2. For those patients from China who are in Global cohort, final DCO and DBL will be when the China tail conducts its final DCO and DBL.

All SAEs that occur in patients still receiving MEDI4736/tremelimumab treatment (or within the 90 days following the last dose of MEDI4736/tremelimumab treatment) post the final DCO and database closure must be reported as detailed in Section 6.4

## **6.2 Definitions of serious adverse event**

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, or follow-up) that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see [Appendix A](#).

## **6.3 Recording of adverse events**

### **6.3.1 Time period for collection of adverse events**

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

### **6.3.2 Follow-up of unresolved adverse events**

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### **6.3.3 Variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported

- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 6.1.1
- Description of the AE

The grading scales found in the revised NCI CTCAE Version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE Version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (<http://ctep.cancer.gov>).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but it is not an SAE unless it meets the criteria

shown in Section 6.2 On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be an SAE if it satisfies the criteria shown in Section 6.2

## 6.4 Reporting of serious adverse events

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

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

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

For fatal or life-threatening AEs in which important or relevant information is missing, active follow-up is undertaken immediately. The Investigator or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, i.e. immediately, but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigator or other site personnel indicates that an AE is serious in the WBDC system, an automated e-mail alert is sent to the designated AstraZeneca representative.

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

After the final DCO for the study, any SAEs occurring whilst the patient is either still receiving MEDI4736 or MEDI4736 + tremelimumab or in the 90 day safety follow up period after receiving the last dose of MEDI4736 or MEDI4736+tremelimumab are to be recorded in a paper form and reported directly 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.

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

The reference documents for the definition of expectedness or listedness are the IBs for MEDI4736 and tremelimumab.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

## 6.5 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

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

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESI/imAEs observed with anti PD-L/PD-1 agents such as MEDI4736 and MEDI4736 in combination with tremelimumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the MEDI4736 and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see [Section 6.10](#)). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 6.4

## 6.6 Overdose

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of IP, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

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

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

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

For patients randomized to the SoC arm, please refer to the local prescribing information for the treatment of cases of overdose. If any overdose is attributed to an AE or SAE please record the AE/SAE diagnosis or symptoms in addition to action taken in the relevant AE modules only of the eCRF.

## 6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- Pregnancy discovered before the study subject has received any study drugs.
- Pregnancy of a female partner of male subject, providing there is no restriction of male subject fathering a child.

### 6.7.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital

abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

### **6.7.2 Paternal exposure**

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

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 alone, whichever is the longer time period should, if possible, be followed up and documented.

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

## **6.8 Study governance and oversight**

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 30 patients have been randomized, whichever occurs first, to review safety assessments and make recommendations to continue,

amend, or stop the study based on safety findings. The committee will meet approximately at every 6 months thereafter.

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

## **6.9 Medication Error**

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error and within 30 days for all other medication errors.

The definition of a Medication Error can be found Appendix A ([A 1](#))

## **6.10 Management of IP-related toxicities**

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, Version 4.03.

### **6.10.1 Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab**

Comprehensive toxicity management guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors, durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune mediated reactions,



infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document entitled, “Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune-Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy),” and is maintained within the Site Master File. In addition, a current version of TMGs is available through the following link: [CCI \[REDACTED\]](#). Please contact the clinical study associate for information on how to gain access to this website.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune-related. In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see [Section 3.9](#) of this protocol and the TMGs). Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting Investigator.

#### **6.10.2 Specific toxicity management and dose modification information – Standard of Care**

Investigators should follow local standard clinical practice regarding dose modifications for agents used in the SoC arm. For specific information regarding the individual agent used in this study, please refer to the local prescribing information for the relevant agent.

## 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

### 7.1 Identity of investigational product(s)

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

**Table 8 List of investigational products for this study**

| Investigational product  | Dosage form and strength | Manufacturer    |
|--------------------------|--------------------------|-----------------|
| MEDI4736                 | 50 mg/mL, solution, IV   | MedImmune       |
| Tremelimumab             | 20 mg/mL, solution, IV   | MedImmune       |
| SoC                      |                          |                 |
| Paclitaxel <sup>a</sup>  | IV (as sourced locally)  | Sourced locally |
| Carboplatin <sup>a</sup> | IV (as sourced locally)  | Sourced locally |
| Gemcitabine <sup>a</sup> | IV (as sourced locally)  | Sourced locally |
| Cisplatin <sup>a</sup>   | IV (as sourced locally)  | Sourced locally |
| Pemetrexed <sup>a</sup>  | IV (as sourced locally)  | Sourced locally |

<sup>a</sup> Under certain circumstances when local sourcing is not feasible, a SoC treatment may be supplied centrally through AstraZeneca

#### 7.1.1 MEDI4736

MEDI4736 will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

#### Preparation of MEDI4736 doses for administration with an intravenous bag

Preparations are to be in accordance with the study-specific drug handling instructions.

#### 7.1.2 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400 mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine-hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate and 0.02% (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be

frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

### **Product preparation and reconstitution of tremelimumab**

Preparations are to be in accordance with the study-specific drug handling instructions.

#### **7.1.3 Standard of Care treatment**

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

### **7.2 Dose and treatment regimens**

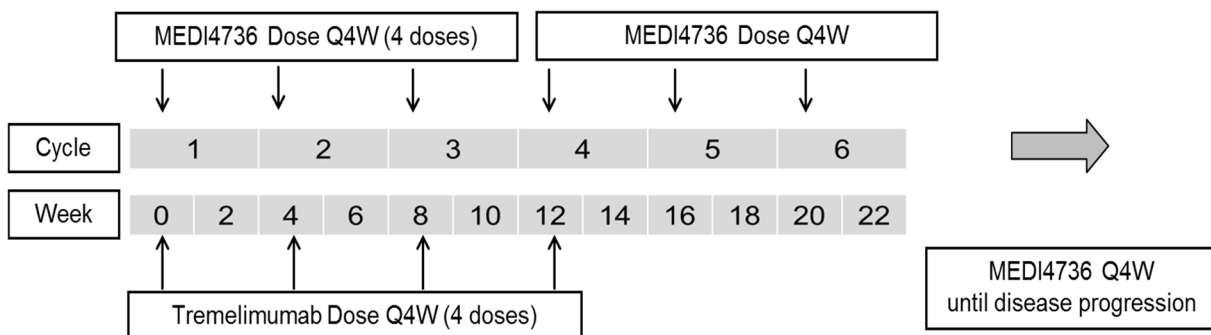
Patients will be randomized in a 1:1 ratio to receive treatment with MEDI4736 + tremelimumab combination therapy or SoC.

#### **7.2.1 Treatment regimens**

##### **MEDI4736 + tremelimumab combination therapy**

Patients in the MEDI4736 + tremelimumab combination therapy group will receive 20-mg/kg MEDI4736 via IV infusion q4w for up to 4 doses/cycles and 1-mg/kg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 20-mg/kg MEDI4736 q4w starting on Week 16 (see [Figure 3](#)). Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. MEDI4736 infusion will start approximately 1 hour after the end of tremelimumab infusion. Standard infusion time for each drug is 60 minutes ( $\pm$  5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The duration will be approximately 1 hour for an infusion. A 1-hour observation period is recommended after the first infusion of MEDI4736 and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each MEDI4736 and tremelimumab infusion).

**Figure 3** **MEDI4736 + tremelimumab combination therapy dosing scheme**



Q4W: every 4 weeks.

### Standard of Care treatment

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

- Paclitaxel + carboplatin: Paclitaxel 200 mg/m<sup>2</sup> and carboplatin area under the curve (AUC) 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m<sup>2</sup> via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m<sup>2</sup> via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Gemcitabine + carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m<sup>2</sup> via IV infusion on Days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD
- Pemetrexed + cisplatin (non-squamous patients only): Pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy
- Pemetrexed + carboplatin (non-squamous patients only): Pemetrexed 500 mg/m<sup>2</sup> and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD. Non-squamous patients who have not progressed after 4 cycles will be eligible for pemetrexed maintenance therapy

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

In addition to CR and PR, a confirmatory scan is always required following the initial demonstration of PD for all patients in the SoC group, even if a subsequent treatment is started.

### **7.2.2 Duration of treatment and criteria for treatment through progression and for retreatment**

All treatment will be administered beginning on Day 1 and all patients in all groups will continue therapy until disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

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

At the Investigator's discretion, patients in all groups may continue receiving therapy in the setting of unconfirmed PD, until confirmed PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. In patients who are clinically stable, a confirmatory scan is required following an overall radiologic time point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

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

Patients in the MEDI4736 (MEDI4736) + tremelimumab combination therapy arm meeting the retreatment criteria below, will follow the same treatment guidelines followed during the initial treatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Retreatment is not permitted for patients in the SoC arm.

Patients who meet the criteria for retreatment may only receive retreatment once.

Crossover within the study will not be permitted.

Patients randomized to the durvalumab (MEDI4736) + tremelimumab combination therapy arm may undergo retreatment as described below:

- Patients who complete the 4 dosing cycles of the combination of MEDI4736 (MEDI4736) and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab (MEDI4736) monotherapy portion of the combination regimen, with or

without confirmation according to RECIST 1.1, may restart treatment with the combination

For all patients who are treated through progression and for patients who are restarting durvalumab (MEDI4736) + tremelimumab, the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status to >1
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention
- The patient still fulfills the eligibility criteria for this study (see Section 3.1 and 3.2). Patients must also agree to re-consenting to restart durvalumab (MEDI4736) + tremelimumab combination therapy

Patients in the immunotherapy arm(s) will not be permitted to continue immunotherapy if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions) i.e. the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period.

Patients who AstraZeneca and the Investigator determine may not continue treatment after PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

### **Post Data Cut Off (DCO)**

For patients continuing to receive MEDI4736 or MEDI4736 + tremelimumab treatment following the scheduled DCO for final analysis of the global cohort, it is recommended that the patients continue the scheduled site visits. For those patients from China who are in the Global cohort, final DCO and DBL will be when the China cohort conducts its final DCO and final DBL.

Based on the analysis results of the global cohort, a decision was made to move the following patients of global cohort to a roll over study

- Patients who are still receiving study treatment (MEDI4736/tremelimumab treatment)

- Patients who were receiving study treatment (MEDI4736/tremelimumab treatment) and are now being followed up for survival

No further data collection in to the Neptune study database is required until the patients in global cohort (with the exception of patients from China) are transitioned to a roll over study. Survival data of patients who are ongoing on MEDI4736/tremelimumab treatment or in follow up after discontinuation of the MEDI4736/tremelimumab treatment, should be documented in patient records. Upon enrolment into the roll over study these data may be retrieved.

All SAEs that occur in patients still receiving MEDI4736/tremelimumab treatment (or within the 90 days following the last dose of MEDI4736/tremelimumab treatment) post the final DCO and database closure must be reported as detailed in Section 6.4

Patients moving to the roll over study will require a new Informed Consent. The OS data collected in the roll over study may be combined with the OS data from NEPTUNE and evaluated as a combined dataset.

### 7.3 Labeling

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

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

**Japan and other countries where this is applicable:** Labels will be prepared in accordance with Good Clinical Practice (GCP) Ordinance. Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.

### 7.4 Storage

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all IP is stored in a secured area, in refrigerated temperatures (2°C to 8°C) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

### 7.5 Compliance

The administration of all IPs should be recorded in the appropriate sections of the eCRF.

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

## 7.6 Accountability

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

Drug accountability should be performed until the patient stops IP completely. Study site personnel will account for all IPs received at the site, for all unused IPs, and for appropriate destruction of IPs. Certificates of delivery, destruction, and return should be signed.

## 7.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the 90 day follow up period following the last dose of study drug. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to section 6.10 for guidance on management of IP-related toxicities.

| <b>Prohibited medication/class of drug:</b>  | <b>Usage:</b>  |
|--|--|
| For all treatment arms   |  |
| Any investigational anticancer therapy other than those under investigation in this study  | Should not be given concomitantly whilst the patient is on study treatment   |
| mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study   | Should not be given concomitantly whilst the patient is on study treatment   |
| Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic therapy, or hormonal therapy for cancer treatment other than those under investigation in this study | Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy]) |
| Live attenuated vaccines   | Should not be given through 30 days after the last dose of IP  |
| For the MEDI4736 ± tremelimumab treatment arms only  |  |



| <b>Prohibited medication/class of drug:</b>  | <b>Usage:</b>  |
|--|--|
| <p>Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor <math>\alpha</math> blockers</p> | <p>Should not be given concomitantly or used for premedication prior to the I-O infusions. The following are allowed exceptions:</p> <ul style="list-style-type: none"> <li>• Use of immunosuppressive medications for the management of IP-related AEs</li> <li>• Short-term premedication for patients expected to receive SoC where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions</li> <li>• Use in patients with contrast allergies</li> <li>• In addition, use of inhaled, topical, and intranasal corticosteroids is permitted</li> </ul> <p>A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.)</p> |
| <p>Drugs with laxative properties and herbal or natural remedies for constipation</p>  | <p>Should be used with caution through to 90 days after the last dose of tremelimumab during the study</p>   |
| <p>Sunitinib</p>   | <p>Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with tremelimumab + sunitinib combination therapy)</p>  |
| <p>EGFR TKIs</p>   | <p>Should not be given concomitantly whilst the patient is on study treatment.</p> <p>In addition, they should be used with caution in the 90 days after the last dose of MEDI4736. (Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when MEDI4736 has been given concomitantly).</p>  |
| <p>Herbal and natural remedies which may have immune-modulating effects</p>  | <p>Should not be given concomitantly unless agreed by the sponsor</p>  |

| <b>Rescue/supportive medication/class of drug:</b>   | <b>Usage:</b>  |
|--|--|
| Concomitant medications or treatments (e.g., 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 [including palliative radiotherapy, etc.])                              | Should be used when necessary for all patients       |
| Inactivated viruses, such as those in the influenza vaccine  | Permitted  |

### 7.7.1 Other concomitant treatment

Medications other than those described in Section 7.7 that are considered necessary for the patient’s safety and well-being may be given at the discretion of the Investigator and should be recorded in the appropriate sections of the eCRF.

### 7.7.2 MEDI4736 drug-drug interactions

There is no information to date on drug-drug interactions with MEDI4736 either pre-clinically or in patients. As MEDI4736 is a monoclonal antibody and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that MEDI4736 will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions. The mechanism of action of MEDI4736 involves binding to PD-L1, and therefore significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

## 7.8 Post study access to study treatment

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving MEDI4736 + tremelimumab combination therapy (see Section 7.2.2). Patients will continue to receive study treatment until they are transitioned to the roll over study.

### 7.8.1 Special roll over study

- These are available for patients remaining in this study after analysis finalized, they can be transferred to such umbrella protocol.
- Roll over study must be fully approved by Regulatory and Ethics bodies applicable for patient’s site.

- Such a study would ensure proper treatment continuation with visits assessment per its protocol.
- Visit assessments will cover the minimum information required for safety oversight and may cover assessments required for long term use analysis.
- Any patient that would be proposed to move to such study, would be required to sign a new Informed Consent Form.

## **8. STATISTICAL ANALYSIS BY ASTRAZENECA**

### **8.1 Statistical considerations**

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

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data. The primary aim of the study is to compare the efficacy and safety of MEDI4736 in combination with tremelimumab to SoC.

Section 8.2 to 8.5 describes the statistical analysis that applies to the global cohort data. For the China cohort, the same definitions of outcome measures (Section 8.4 on Outcome measures) and methods of statistical analysis (Section 8.5) will be applied unless specified in Section 8.6 or the China specific SAP.

### **8.2 Sample size estimate**

The study will plan to enroll approximately 1330 patients in order to randomize 800 eligible patients 1:1 to MEDI4736 + tremelimumab combination therapy or SoC globally. The 800 patients will comprise approximately 336 patients who have PD-L1-positive<sub>25%</sub> tumors and approximately 520 patients who have PD-L1-positive<sub>1%</sub> tumours. Global recruitment will be complete once approximately 800 patients have been randomized of which 30 patients are from mainland China. Once global enrollment is completed, the recruitment will continue in mainland China only. A total of approximately 160 patients from mainland China will be randomized (refer to Section 8.6 for more details).

The primary analysis will be performed when approximately 87% maturity in the population with bTMB  $\geq 20$  mut/Mb is achieved.

The sample size calculation assumes a 3-month delay in separation of the OS curves between each group and with a 12-month recruitment period and a minimum follow up period of 43 months assumed, it is anticipated that this analysis will be performed 55 months after the first patient has been recruited. The true OS average hazard ratios (HR) in bTMB $\geq 20$ ,  $\geq 16$ ,  $\geq 12$ , and PD-L1 negative population are based on observation from D419AC00001 study, as well as based on what would be considered a clinically meaningful improvement in the biomarker

selected population. The expected number of patients and prevalence in this study are based on observation from D419AC00001 study.

#### **MEDI4736 + tremelimumab versus SoC (OS in bTMB $\geq$ 20 mut/Mb population)**

Assuming the true OS average hazard ratio (HR) is 0.49 and the median OS in SoC chemotherapy alone arm is 10 months following an exponential distribution for both MEDI4736 + tremelimumab and SoC arm in the bTMB $\geq$ 20 mut/Mb population, with approximately 140 patients, 122 OS events from the global cohort (approximately 87% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha overall level of 5%. The smallest treatment difference that is statistically significant will be an HR of 0.70.

#### **MEDI4736 + tremelimumab versus SoC (OS in bTMB $\geq$ 16 mut/Mb population)**

Assuming the true OS average HR is 0.62 and the median OS in SoC chemotherapy alone arm is 10 months following an exponential distribution for both MEDI4736 + tremelimumab and SoC arm in the bTMB $\geq$ 16 mut/Mb population, with approximately 212 patients, 193 OS events from the global cohort (approximately 91% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha overall level of 5%. The smallest treatment difference that is statistically significant will be an HR of 0.75.

#### **MEDI4736 + tremelimumab versus SoC (OS in bTMB $\geq$ 12 mut/Mb population)**

Assuming the true OS average HR is 0.65 and the median OS in SoC chemotherapy alone arm is 10 months following an exponential distribution for both MEDI4736 + tremelimumab and SoC arm in the bTMB $\geq$ 12 mut/Mb population, with approximately 304 patients, 280 OS events from the global cohort (approximately 92% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha overall level of 5%. The smallest treatment difference that is statistically significant will be an HR of 0.79.

#### **MEDI4736 + tremelimumab versus SoC (OS in PD-L1 negative population)**

Assuming the true OS average HR is 0.73 and the median OS in SoC chemotherapy alone arm is 10 months following an exponential distribution for both MEDI4736 + tremelimumab and SoC arm in the PD-L1 negative population, with approximately 194 patients, 182 OS events from the global cohort (approximately 94% maturity) will provide 57% power to demonstrate statistical significance at the 2-sided alpha overall level of 5%. The smallest treatment difference that is statistically significant will be an HR of 0.75.

### **8.3 Definitions of analysis sets**

Definitions of the analysis sets for each outcome variable are provided in [Table 9](#).

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

| <b>Outcome variable</b>               | <b>Population</b>                    |
|---------------------------------------|--------------------------------------|
| <b>Efficacy data</b>                  |                                      |
| OS                                    | bTMB $\geq$ 20 mut/Mb analysis set   |
| OS                                    | bTMB $\geq$ 16 mut/Mb analysis set   |
| OS                                    | bTMB $\geq$ 12 mut/Mb analysis set   |
| OS                                    | PD-L1-negative analysis set          |
| OS                                    | FAS (ITT population)                 |
| OS                                    | bTMB < 20 mut/Mb analysis set        |
| OS                                    | bTMB non-evaluable analysis set      |
| OS                                    | PD-L1 $\geq$ 25%                     |
| OS                                    | PD-L1 $\geq$ 50%                     |
| OS                                    | tTMB cutoff-based analysis sets      |
| PFS, ORR                              | bTMB $\geq$ 20 mut/Mb analysis set   |
| PFS, ORR                              | bTMB $\geq$ 16 mut/Mb analysis set   |
| PFS, ORR                              | bTMB $\geq$ 12 mut/Mb analysis set   |
| PFS, ORR                              | PD-L1-negative analysis set          |
| PFS, ORR                              | FAS (ITT population)                 |
| PFS, ORR                              | PD-L1 $\geq$ 25%                     |
| PFS, ORR                              | PD-L1 $\geq$ 50%                     |
| PFS, ORR                              | tTMB cutoff-based analysis sets      |
| APF12, OS12, OS18, OS24 and PFS2, DoR | bTMB $\geq$ 20 mut/Mb analysis set   |
| APF12, OS12, OS18, OS24 and PFS2, DoR | bTMB $\geq$ 16, mut/Mb analysis sets |
| APF12, OS12, OS18, OS24 and PFS2, DoR | bTMB $\geq$ 12 mut/Mb analysis set   |
| APF12, OS12, OS18, OS24 and PFS2, DoR | PDL1-negative analysis set           |
| APF12, OS12, OS18, OS24 and PFS2, DoR | FAS (ITT population)                 |
| Demography                            | FAS (ITT population)                 |
| PK data                               | PK analysis set                      |
| <b>Safety Data</b>                    |                                      |
| Exposure                              | Safety Analysis Set                  |
| AEs                                   | Safety Analysis Set                  |
| Laboratory measurements               | Safety Analysis Set                  |
| Vital signs                           | Safety Analysis Set                  |

| Outcome variable | Population          |
|------------------|---------------------|
| ECGs             | Safety Analysis Set |

FAS: Full analysis set

### 8.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients prior to the end of global recruitment. Any patients recruited in China, after global recruitment has ended, will not be included in the FAS (see Section 8.6). China patients will not undergo bTMB analysis and testing and details of the analysis of this population will be described in the China specific SAP. Treatment groups will be compared on the basis of randomized IP, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive IP are included in the analysis in the treatment group to which they were randomized.

### 8.3.2 bTMB $\geq 20$ mut/Mb analysis set

The bTMB  $\geq 20$  mut/Mb analysis set will include the subset of patients in the FAS whose blood TMB status is  $\geq 20$  mut/Mb as defined by the CCI [REDACTED]

### 8.3.3 bTMB $\geq 16$ mut/Mb analysis set

The bTMB  $\geq 16$  mut/Mb analysis set will include the subset of patients in the FAS whose blood TMB status is  $\geq 16$  mut/Mb as defined by the CCI [REDACTED].

### 8.3.4 bTMB $\geq 12$ mut/Mb analysis set

The bTMB  $\geq 12$  mut/Mb analysis set will include the subset of patients in the FAS whose blood TMB status is  $\geq 12$  mut/Mb as defined by the CCI [REDACTED].

### 8.3.5 bTMB non-evaluable analysis set

The bTMB non-evaluable analysis set will include the subset of patients in the FAS

- Whose blood TMB status cannot be determined by the CCI [REDACTED]
- Whose sample for evaluation of bTMB is not available

### 8.3.6 PD-L1-negative analysis set

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

### **8.3.7 tTMB - based analysis sets**

Methods for determining analysis sets based on tissue TMB will be defined in the SAP. Cutoffs for tTMB-based analysis sets will be based on data collected outside of this study, independent of the data collected for Neptune.

### **8.3.8 Safety analysis set**

The safety analysis set (SAS) will consist of all patients including those patients recruited prior to the end of global recruitment who received at least 1 dose of IP. Any patients recruited in China, after global recruitment has ended, will not be included in the safety analysis set (see Section 8.6). Safety data will not be formally analyzed but summarized using the SAS, according to the treatment received, that is, erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

### **8.3.9 Pharmacokinetic analysis set**

All patients who received at least 1 dose of IP per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analysis will be included in the PK analysis set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analysis being performed.

## **8.4 Outcome measures for analysis**

### **8.4.1 Calculation or derivation of efficacy variables**

This study will analyze the primary endpoint of OS. In addition, the analysis of the secondary endpoints of PFS, ORR, DoR, and APF12 will be based on Investigator tumor assessments according to RECIST 1.1. PFS2 will be defined by local clinical practice, and survival rate (OS12, OS18 and OS24) will also be analyzed.

#### **Primary endpoint - overall survival**

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

Note: Survival calls will be made following the date of data cut-off for the analysis (these contacts should generally occur within 7 days of the data cut off). If patients are confirmed to be alive or if the death date is post the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries.

The Kaplan-Meier estimates of OS12, OS18, OS24 (survival rate, that is, proportion of patients alive at 12, 18 and 24 months) will also be derived as secondary endpoints.

#### **8.4.1.1 Investigator RECIST 1.1-based endpoints**

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues IP or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression in which case the response will be assigned as PD).

The definitions of CR, PR, SD, and PD are given in [Appendix D](#).

#### **8.4.1.2 Secondary endpoints**

##### **Progression-free survival**

PFS (per RECIST 1.1 using Investigator assessments) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 or more missed visits. If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 visits of baseline.

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

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

- For investigational assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment

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

PFS based on RECIST 1.1 modified for confirmation of progression will be performed for exploratory purposes using the algorithm described above for the RECIST 1.1 Investigator



assessments, but following a modification whereby any objective disease progression must be confirmed by the next scheduled scan. The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression and preferably at the next scheduled visit. If disease progression is confirmed (or disease progression occurs and no further scans are recorded) then the date of progression will be when it was originally observed. Patients with a single disease progression and no further tumor assessment scans will be treated as PD in the analysis. In the absence of significant clinical deterioration, the investigational site is advised to continue the patient on their randomized MEDI4736 + tremelimumab combination therapy until progression has been confirmed. If progression is not confirmed, the patient should continue their randomized MEDI4736 + tremelimumab combination therapy and on-treatment assessments. In the SoC arm, treatment through PD, until PD is confirmed is at the Investigator's discretion; however, a confirmatory scan is required for all patients in the SoC group, even if a subsequent treatment is started.

### **Objective response rate**

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

### **Duration of response**

DoR (per RECIST 1.1 using Investigator assessments) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

### **Proportion of patients alive and progression free at 12 months from randomization**

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

### **Time from randomization to second progression**

PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Second progression status will be reviewed (q6w for the first 48 weeks relative to the date of randomization and then q8w thereafter) following the progression event used for the primary variable PFS (the first progression) and status

recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, that is, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

### **Best objective response**

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in [Appendix D](#). It is the best response a patient has had during their time in the study up until RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorization of BoR will be based on RECIST ([Appendix D](#)) using the following response categories: CR, PR, SD, PD, and NE.

BoR will be determined programmatically based on RECIST using all Investigator assessments up until the first progression event. For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs  $\leq 90$  days (i.e.,  $2 \times (6 \text{ weeks} \pm 3 \text{ days})$ ) after randomization, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs  $> 90$  days (ie,  $2 \times (6 \text{ weeks} \pm 3 \text{ days})$ ) after the date of randomization then BoR will be assigned to the NE category.

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

## **8.4.2 Calculation or derivation of safety variables**

### **8.4.2.1 Adverse events**

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of the last dose of MEDI4736 + tremelimumab combination therapy or within 30 days of the last dose of SoC may be included in the AE summaries, but the majority of those summaries will omit those AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

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

#### **8.4.2.2 Other significant adverse events**

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

#### **8.4.2.3 Safety assessments**

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of IP.

The QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT).

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

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

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

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs data should include only those patients with recorded data.

### **8.4.3 Calculation or derivation of pharmacokinetic variables**

#### **8.4.3.1 Population pharmacokinetics and exposure-response/safety analysis**

A population PK model will be developed using a non-linear mixed-effects modeling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy

data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

#### **8.4.3.2 Pharmacokinetic non-compartmental analysis**

The PK analysis will be performed at AstraZeneca. The actual sampling times will be used in the PK calculations. PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow). Samples below the lower limit of quantification will be treated as missing in the analysis.

#### **8.4.3.3 Immunogenicity analysis**

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against MEDI4736 and tremelimumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

#### **8.4.4 Calculation or derivation of biomarker variables**

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

### **8.5 Methods for statistical analysis**

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

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

The primary endpoint is OS in patients with bTMB  $\geq 20$  mut/Mb tumors. The study has been sized to characterize the OS benefit of MEDI4736 + tremelimumab combination therapy versus SoC. The analysis will be performed when:

- approximately 87% maturity in the bTMB  $\geq 20$  mut/Mb analysis set is achieved

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group.

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

All data collected will be listed. Efficacy data will be summarized and analyzed based on the bTMB  $\geq 20$  mut/Mb analysis set, bTMB  $\geq 16$  mut/Mb analysis set, bTMB  $\geq 12$  mut/Mb analysis set and the PDL1-negative analysis set, FAS, PDL1  $\geq 25\%$ , PDL1  $\geq 50\%$  and tTMB-based analysis sets. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized based on the Safety Analysis Set.

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

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

**Table 10 Pre-planned statistical and sensitivity analysis to be conducted**

| Endpoints analyzed | Notes  |
|--------------------|--|
| OS                 | <p><u>log-rank test for:</u></p> <p>Primary analysis in:</p> <ul style="list-style-type: none"> <li>• bTMB <math>\geq 20</math> mut/Mb analysis set</li> </ul> <p>Secondary analysis in:</p> <ul style="list-style-type: none"> <li>• bTMB <math>\geq 16</math> mut/Mb analysis set</li> <li>• bTMB <math>\geq 12</math> mut/Mb analysis set</li> <li>• PDL1-negative analysis set</li> <li>• FAS (ITT population)</li> <li>• bTMB <math>&lt; 20</math> mut/Mb analysis set</li> <li>• bTMB non-evaluable analysis set</li> <li>• PD-L1 <math>\geq 25\%</math></li> <li>• PD-L1 <math>\geq 50\%</math></li> <li>• tTMB cutoff-based analysis set</li> </ul> <p>Weighted log-rank test for primary analysis in:</p> <ul style="list-style-type: none"> <li>• bTMB <math>\geq 20</math> mut/Mb analysis set</li> </ul> |

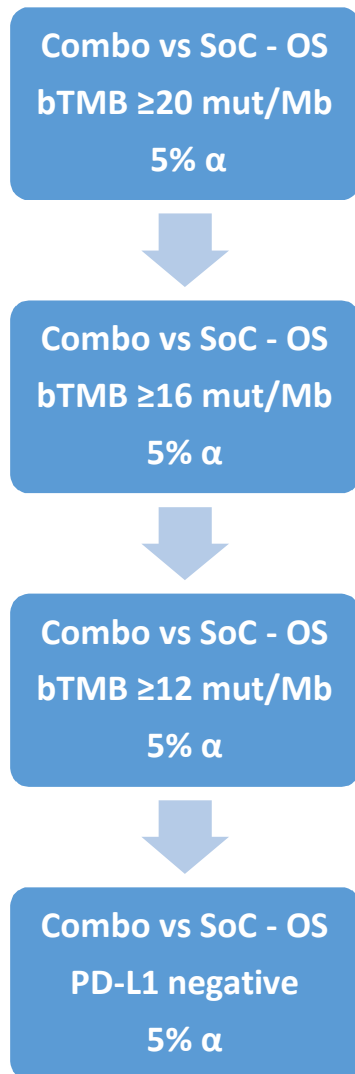
| Endpoints analyzed  | Notes   |
|---------------------|---|
| OS12, OS18 and OS24 | <p>HR using the Kaplan-Meier estimates of survival rate at 12 months, 18 months and 24 months (following method described by <a href="#">Klein et al 2007</a>) in:</p> <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 20 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 16 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 12 mut/Mb analysis set</li> <li>• PDL1-negative analysis set</li> <li>• FAS (ITT population)</li> <li>• tTMB cutoff based analysis set</li> </ul>  |
| PFS                 | <p><u>Log-rank tests for:</u></p> <ul style="list-style-type: none"> <li>• Investigator RECIST 1.1 assessments in:</li> <li>• bTMB <math>\geq</math> 20 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 16 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 12 mut/Mb analysis set</li> <li>• PDL1-negative analysis set</li> <li>• FAS (ITT population)</li> <li>• PD-L1 <math>\geq</math> 25%</li> <li>• PD-L1 <math>\geq</math> 50%</li> <li>• tTMB cutoff-based analysis sets</li> </ul> <p>Sensitivity analysis based on RECIST 1.1 modified for confirmation of progression using Investigator assessments</p> |
| ORR                 | <p><u>Logistic regression for:</u></p> <ul style="list-style-type: none"> <li>• Secondary analysis using Investigator RECIST 1.1 assessments in:</li> <li>• bTMB <math>\geq</math> 20 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 16 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 12 mut/Mb analysis set</li> <li>• PDL1-negative analysis set</li> <li>• FAS (ITT population)</li> <li>• PD-L1 <math>\geq</math> 25%</li> <li>• PD-L1 <math>\geq</math> 50%</li> <li>• tTMB cutoff-based analysis sets</li> </ul>   |

| Endpoints analyzed | Notes   |
|--------------------|---|
| DoR                | <u>Analysis methods as described by Ellis et al 2008 for:</u> <ul style="list-style-type: none"> <li>• Secondary analysis using Investigator assessments (RECIST 1.1) in:</li> <li>• bTMB <math>\geq</math> 20 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 16 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 12 mut/Mb analysis set</li> <li>• PDL1-negative analysis set</li> <li>• FAS (ITT population)</li> </ul> |
| APF12              | HR using the Kaplan-Meier estimates of PFS at 12 months (following method described by Klein et al 2007) in: <ul style="list-style-type: none"> <li>• <math>\geq</math> bTMB <math>\geq</math> 20 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 16 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 12 mut/Mb analysis set</li> <li>• PDL1-negative analysis set</li> <li>• FAS (ITT population)</li> </ul>              |
| PFS2               | <u>Log-rank test in:</u> <ul style="list-style-type: none"> <li>• bTMB <math>\geq</math> 20 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 16 mut/Mb analysis set</li> <li>• bTMB <math>\geq</math> 12 mut/Mb analysis set</li> <li>• PDL1-negative analysis set</li> <li>• FAS (ITT population)</li> </ul>  |

### Multiple testing strategy

In order to strongly control the type I error at 5% 2-sided, a multiple testing procedure (MTP) with gatekeeping strategy will also be used across the primary endpoints (OS) in the bTMB  $\geq$  20 mut/Mb populations and key secondary endpoint bTMB  $\geq$  16 mut/Mb, bTMB  $\geq$  12 mut/Mb, OS in PD-L1-negative analysis population. If the higher level hypothesis in the MTP is rejected for superiority, the following hypothesis will then be tested in the MTP as shown in [Figure 4](#).

**Figure 4** Multiple testing procedures for controlling the type I error rate



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

#### 8.5.1 Analysis of primary endpoint - overall survival

The primary OS analysis will be performed in the  $bTMB \geq 20$  mut/Mb populations using a log-rank test. The effect of MEDI4736 + tremelimumab combination therapy versus SoC treatment will be estimated by the HR together with its appropriately sized CI and p-value.

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

Kaplan-Meier plots of OS will be presented by treatment group, and by treatment group and PD-L1 tumor status subgroup, where appropriate. Summaries of the number and percentage of



patients who have died, who are still in survival follow-up, who are lost to follow-up, and who have withdrawn consent will be provided along with the median OS for each treatment.

Secondary analysis of OS will be performed to compare MEDI4736 + tremelimumab combination therapy versus SoC in the bTMB  $\geq 16$  mut/Mb, bTMB  $\geq 12$  mut/Mb and PD-L1 negative analysis sets, and analysis sets mentioned in [Table 10](#) using a log-rank test. The analysis in PD-L1-negative population will be performed using a stratified log-rank test adjusting only for histology (squamous versus non-squamous) and smoking status. The effect of treatment will be estimated by the HR together with its appropriately sized CI and p-value. The HR and CI will be estimated using the Cox proportional hazards model.

Subgroup analysis will be conducted comparing OS between MEDI4736 + tremelimumab combination therapy versus SoC in the following subgroups of primary population (TMB  $\geq 20$  mut/Mb) and FAS analysis sets as deemed appropriate (but not limited to):

- Sex (male versus female)
- Age at randomization (<65 versus  $\geq 65$  years of age)
- Histology (squamous versus non-squamous)
- Smoking status (never smoker versus ever smoker)
- Race (Asian versus non-Asian)
- bTMB ( $\geq 12$  versus  $< 12$  mut/Mb,  $\geq 16$  versus  $< 16$  mut/Mb, ( $\geq 20$  versus  $< 20$  mut/Mb) , bTMB evaluable vs non-evaluable population. (FAS only)
- PD-L1 using cutpoints of 1%, 10%, 25% and 50% tumour expression ( $\geq 1\%$  versus  $< 1\%$ ,  $< 10\%$  versus  $\geq 10\%$ ,  $\geq 25\%$  versus  $< 25\%$  and  $< 50\%$  versus  $\geq 50\%$ ) and immune cell expression (IC  $\geq 25\%$  versus  $< 25\%$ )
- ECOG (0 versus 1)
- Baseline Liver Metastases (Yes versus No)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment groups. The purpose of the subgroup analysis is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

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

Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. For the bTMB -based analysis sets, a model will be constructed, containing treatment alone, to ensure that any output from the Cox modeling is likely to be consistent

with the results of the log-rank test. For PDL1-based analysis set and the FAS, the model will contain treatment and stratification factors, to be consistent with the results of the stratified log-rank test.

Interactions between treatment and stratification factor will also be tested to rule out any qualitative interaction using the approach of [Gail and Simon 1985](#).

Additionally, for each subgroup, the HR (MEDI4736 + tremelimumab combination therapy: SoC) and appropriately sized CI will be calculated from a single model that contains treatment and subgroup factor. These will be presented on a forest plot including the HR and 95% CI.

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

### **8.5.2 Progression-free survival**

The main PFS analysis will be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments in the bTMB  $\geq 20$ , bTMB  $\geq 16$ , bTMB  $\geq 12$ , and PDL1-negative analysis sets, and analysis sets mentioned in [Table 10](#) for the PFS endpoint. PFS will be analyzed using a log-rank test, using the same methodology described for the OS endpoint. The effect of MEDI4736 + tremelimumab combination therapy versus SoC will be estimated by the HR together with its corresponding CI and p-value.

Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment.

Sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analyzed using a log-rank test. For patients whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust even in highly asymmetric assessment schedules ([Sun and Chen 2010](#)).

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

Secondary analysis of PFS based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments will be performed to compare MEDI4736 + tremelimumab combination therapy versus SoC in the bTMB based analysis sets and in the PD-L1-negative

population, and analysis sets mentioned in [Table 10](#). This analysis will be performed using a log-rank test in the bTMB analysis sets, and a stratified log-rank test adjusting only for histology (squamous versus non-squamous) and smoking status in the PD-L1-negative population. The effect of treatment will be estimated by the HR together with its corresponding appropriately sized CI and p-value. The HR and CI will be estimated using the same approach as specified above for the primary analysis of OS. Details will be included in the SAP.

An exploratory analysis of PFS using Investigator assessment based on RECIST 1.1 modified for confirmation of progression will be performed. The log-rank test used for the primary analysis of PFS will be repeated.

Subgroup analysis will be conducted comparing PFS (per RECIST 1.1 using Investigator assessments) between MEDI4736 + tremelimumab combination therapy versus SoC using the same methodology as described in [Section 8.5.1](#) for the primary endpoint of OS.

### **8.5.3 Objective response rate**

The ORR will be based on the programmatically derived RECIST using the Investigator tumor data. The ORR will be compared between MEDI4736 + tremelimumab combination therapy versus SoC using logistic regression models adjusting for the same factors as the primary endpoint (PD-L1 tumor expression, histology, and smoking status), as appropriate and wherever used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). This analysis will be performed in the analysis sets mentioned in [Table 10](#). The analysis of the patients with PD-L1-negative population tumors will be performed using a logistic regression model adjusting for only histology and smoking status.

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

### **8.5.4 Duration of response**

In order to analyze the DoR between MEDI4736 + tremelimumab combination therapy and SoC, the expected DoR (EDoR) will be derived for each treatment group ([Ellis et al 2008](#)) using the Investigator tumor data. The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients and provides an estimate based on all randomized patients. Treatments will be compared by calculating the ratio of EDoRs, using an appropriate probability distribution (to be specified in the SAP) for DoR in responding patients. Additionally, descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment groups or p-value attached). These analysis will be performed in the analysis sets mentioned for DoR in [Table 10](#).

### 8.5.5 Survival rate at 12 months, 18, and 24 months

OS12, OS18 and OS 24 will be summarized using the Kaplan-Meier curve and presented by treatment group. These landmark survival rates will be compared between MEDI4736 + tremelimumab combination therapy and SoC by using the Kaplan-Meier estimator of OS at corresponding landmark times for each treatment to obtain the HR. The HR and CI will be presented using the following approach (Klein et al 2007):

- The  $HR(\text{group1}:\text{group2})$  is estimated as  $\frac{\ln \hat{S}_1(t)}{\ln \hat{S}_2(t)}$
- The variance for  $\ln(HR)$  is estimated as  $\frac{\hat{\sigma}_1(t)^2}{\ln^2 S_1(t)} + \frac{\hat{\sigma}_2(t)^2}{\ln^2 S_2(t)}$

where  $\hat{\sigma}_i(t)^2 = \sum_{t_i \leq t} \frac{d_i}{n_i(n_i - d_i)}$  is the variance for  $\ln\{S(t)\}$  derived from Greenwood's formula

for the variance of  $S(t)$  and can be estimated from standard software packages, where  $d_i$  and  $n_i$  refer to the number of events and patients at risk for each risk set.

The  $\ln(HR)$  and its variance in each stratum will be estimated and combined by weighting inversely proportionately according to each within stratum variance (Whitehead and Whitehead 1991).

This analysis will be performed in the analysis sets mentioned for OS12, OS18 and OS24 in Table 10.

### 8.5.6 Proportion of patients alive and progression free at 12 months from randomization

The APF12 will be summarized (using the Kaplan-Meier curve) and presented by treatment group. APF12 will be compared between MEDI4736 + tremelimumab combination therapy and SoC by using the same methodology as described for the survival rate at 12 months.

This analysis will be performed in the analysis sets mentioned for APF12 in Table 10.

### 8.5.7 Time from randomization to second progression

Second progression (PFS2) will be analyzed using log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of MEDI4736 + tremelimumab combination therapy versus SoC will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

For supportive purposes, the time to the start of subsequent therapy will be analyzed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan-Meier plot of the time to the start of subsequent therapy

will be presented by treatment group and the time between progression and starting subsequent therapy will be assessed. No multiplicity adjustment will be applied as these are viewed as supportive endpoints.

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

This analysis will be performed in the analysis sets mentioned for PFS2 as mentioned in [Table 10](#).

#### **8.5.8 Safety data**

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

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

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

#### **8.5.9 Pharmacokinetic data**

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

#### **8.5.10 Immunogenicity analysis**

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

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

### **8.5.11 Pharmacokinetic/Pharmacodynamic relationships**

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

### **8.5.12 Biomarker data**

The relationship of PD-L1 expression and bTMB/tTMB, and if appropriate, other exploratory biomarkers (e.g., IFN- $\gamma$ ) with clinical outcomes (including but not restricted to) OS, PFS and ORR may be presented. Cutoffs for these biomarkers will be determined based on data outside of this clinical study.

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

### **8.5.13 Exploratory analysis**

Exploratory analysis of OS adjusting for impact of subsequent therapy may be performed if a sufficient proportion of patients switch. Methods such as Rank Preserving Structural Failure Time (Robins and Tsiatis 1991), Inverse Probability of Censoring Weighting (Robbins 1993) and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be summarized for SoC patients, splitting between those who have and have not switched at the time of the analysis. In addition, OS may be analyzed in centers where crossover does not occur.

## **8.6 China Cohort**

The global cohort has approximately 1330 patients enrolled from sites in North America, Latin America, Asia, Europe, and Gulf countries to randomize approximately 800 patients. The China cohort consists of all Chinese patients from sites accredited by China health authority and enrolled prior to the last patient last visit (LPLV) of the global cohort. The China cohort will have approximately 160 randomized patients. The global cohort consists of all patients recruited by the documented date of last patient first visit (LPFV) of the global cohort. Global recruitment will be complete once approximately 800 patients have been randomized of which 30 patients are from mainland China. Once global enrollment is completed, recruitment across all sites except for those in mainland China will be closed, and the recruitment of China patients will continue until the total number of randomized China patients is reached. Hence, a patient randomized in the China cohort prior to the LPFV of the global cohort enrollment will be included in both the (globally recruited) FAS and the China FAS. A patient randomized in the China cohort after the LPFV of the global cohort enrollment will be included only in the China FAS.

Per China regulatory guidance, in addition to the evaluation of the global cohort data for primary, secondary and safety objectives, evaluation of consistency in efficacy and safety in

China and Asia population is required to facilitate the benefit-risk assessment for Chinese patients. Hence, the safety and efficacy data in the China cohort will be analyzed separately where the same endpoint definitions (as described in Section 8.4) will hold. The primary comparison of OS between the treatment arms in the China cohort will be done on the PD-L1 defined population. Details of this analysis can be found in the China specific SAP.

**The China full analysis set (China FAS)** will include all patients randomized in the China cohort and will be used for all China only efficacy analysis.

**The China safety analysis set** will consist of all patients recruited in the China cohort who received at least one dose of study treatment.

Efficacy analysis for the China cohort will be performed when the OS data from the China patients is of similar maturity where significant clinical efficacy is established in the global cohort, i.e. if OS efficacy is established at the final analysis, a similar maturity to this will be used for consistency evaluation.

All statistical analysis will be considered exploratory and only performed if sufficient numbers of events or patients are available (e.g.  $\geq 20$  OS or PFS events) unless specified, otherwise, descriptive statistics only will be presented. No adjustment for multiplicity will be made and the procedure for hierarchical testing detailed in Section 8.5 will not be followed. OS efficacy evaluation for the China cohort will be performed once.

Details of the China cohort and Asia population analysis, including the vendor to perform the analysis, will be specified in the China supplementary SAP, which is to be finalized before the global cohort data locks for analysis.

## **9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA**

### **9.1 Training of study site personnel**

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

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

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

## **9.2 Monitoring of the study**

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual, and IP accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- Ensure that withdrawal of informed consent for the use of the patient's biological samples is reported, biological samples are identified and disposed of or destroyed accordingly, and the action is documented and reported to the patient

The AstraZeneca representative will be available between visits if the Investigators or other staff at the centers need information and advice about the study conduct.

### **9.2.1 Source data**

Refer to the CSA for the location of source data.

### **9.2.2 Direct access to source data in Japan**

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

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

### **9.2.3 Study agreements**

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to



the conduct of the study and the treatment of patients. In all other respects not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

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

#### **9.2.4 Archiving of study documents**

The Investigator will follow the principles outlined in the CSA.

### **9.3 Study timetable and end of study**

The end of the study is defined as the “last visit of the last patient undergoing the study.” The Investigator will be notified by AstraZeneca when recruitment is complete.

The study is expected to start in Q3 2015 and end by Q2 2020.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP) or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study involving MEDI4736.

### **9.4 Data management by AstraZeneca or delegate**

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

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

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

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

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

#### **Serious adverse event reconciliation**

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

## **Data associated with human biological samples**

Data associated with human biological samples will be transferred from laboratories internal or external to AstraZeneca.

## **10. ETHICAL AND REGULATORY REQUIREMENTS**

### **10.1 Ethical conduct of the study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples. The applicable regulatory requirements in Japan are “Good Clinical Practice for Trials on Drugs” (Ministry of Health, Labor, and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications).

### **10.2 Patient data protection**

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document.

### **10.3 Ethics and regulatory review**

An EC/IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority should be approved, according to local regulations.

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

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

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

### **Japan and other countries where this is applicable:**

An IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as the IRB written approval to AstraZeneca and the Principal Investigator before enrollment of any patient should into the study.

The IRB/EC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF, which are needed to meet local requirements.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds 1 year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will provide regulatory authorities, IRB, the head of the study site, and the PIs with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB, providing the details of all relative safety information reported by AstraZeneca.

## **10.4 Informed consent**

The Principal Investigator(s) at each center will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study

- Ensure that each patient is notified that he or she is free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that each patient provides a signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure that a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB

#### **For sites in Japan only**

If any new information on the IP becomes available that may influence the decision of the patient to continue the study, the Investigator should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue the participation in the study. In addition, if the Investigator deems it necessary to revise the ICF, he or she should revise it immediately (refer to Section 10.5). The Investigator should re-explain to the patients using the updated ICF even if the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

## **10.5 Changes to the protocol and informed consent form**

#### **For sites outside Japan**

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant EC/IRB and, if applicable, the national regulatory authority, before implementation. Local requirements are to be followed for new versions of the Clinical Study Protocol.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to EC/IRB, see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC/IRB are to approve the revised ICF before the revised form is used.

**For Japan sites only:**

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the Clinical Study Protocol to be amended, the new version of the Clinical Study Protocol should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a Clinical Study Protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

**10.6 Audits and inspections**

Authorized representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and to determine if data were recorded, analyzed, and accurately reported according to the protocol, GCPs, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

## 11. LIST OF REFERENCES

### **Alexandrov et al, 2013**

Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, et al. Signatures of mutational processes in human cancer. *Nature*. 2013 Aug 22;500:415-21.

### **Antonia et al 2014a**

Antonia S, Goldberg S, Balmanoukian A, Narwal R, Robbins P, D'Angelo G, et al. A Phase 1 open-label study to evaluate the safety and tolerability of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in combination with tremelimumab in patients with advanced non-small cell lung cancer (NSCLC). Poster presented at European Society of Medical Oncology Meeting; 2014 Sep 26-30; Madrid, Spain.

### **Antonia et al 2014b**

Antonia S, Ou SI, Khleif SN, Brahmer J, Blake-Haskins A, Robbins PB, et al. Clinical activity and safety of MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody in patients with NSCLC. Poster presented at the European Society for Medical Oncology Meeting; 2014 Sep 26-30; Madrid, Spain.

### **Ayers et al 2017**

Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN- $\gamma$ -related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest*. 2017;127:2930-2940.

### **Balar et al Dec 2017**

Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389:67-76. Epub 2016 Dec 8.

### **Bonomi 2010**

Bonomi PD. Implications of key trials in advanced nonsmall cell lung cancer. *Cancer* 2010;116:1155-64.

### **Brahmer et al 2012**

Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455-65.

### **Brahmer et al 2014**

Brahmer JR, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis [ASCO abstract 8112]. *J Clin Oncol* 2014;32(Suppl).

**Burman et al 2009**

Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni-based multiple tests. *Stat Med* 2009;28:739-61.

**Butte et al, 2007**

Butte MJ, Keir ME, Phamduy TB, Freeman GJ, Sharpe AH. PD-L1 interacts specifically with B7-1 to inhibit T cell proliferation. *Immunity*. 2007;27:111-22.

**Carbone et al 2017**

Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;376:2415-26.

**Ciuleanu et al 2009**

Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomized, double-blind, phase 3 study. *Lancet* 2009;374:1432-40.

**Cox 1972**

Cox DR. Regression models and life-tables. *J Royal Stat Society* 1972;Series B 34(2):187-220.

**D'Addario et al 2010**

D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5):116-9.

**Drake et al 2013**

Drake CG, McDermott DF, Sznol M, Choueiri TK, Kluger HM, Powderly JD et al. Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up [abstract 4514]. *J Clin Oncol* 2013;31(Suppl).

**Dunn et al 2004**

Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol* 2004;22:329-60.

**Ellis et al 2008**

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials* 2008;29:456-65.

**Fife and Bluestone, 2008**

Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev*. 2008;224:166-82.

**Forde et al 2014**

Forde PM, Kelly RJ, Brahmer JR. New strategies in lung cancer: translating immunotherapy into clinical practice. *Clin Cancer Res* 2014;20:1067-73.

**Gail and Simon 1985**

Gail M, Simon R. Tests for qualitative interactions between treatment effects and patient subsets. *Biometrics* 1985;41:361–72.

**Gandara et al 2018**

Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, Li Y, Rittmeyer A, Fehrenbacher L, Otto G, Malboeuf C, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med*.2018;24:1441–1448. doi: 10.1038/s41591-018-0134-3.

**Garon et al 2015**

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al, KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer [published online ahead of print April 19, 2015]. *N Engl J Med* 2015. doi:10.1056/NEJMoa1501824.

**Gettinger et al 2015**

Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer [published online ahead of print April 20, 2015]. *J Clin Oncol* 2015;33. doi:10.1200/JCO.2014.58.3708.

**Glimm et al 2010**

Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. *Stat Med* 2010;29:219-28.

**GLOBOCAN 2012**

GLOBOCAN. Lung cancer, estimated incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer, World Health Organization; Lyon, 2012 [cited 16 April 2015]. Available from: URL: [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx).

**Hellmann et al 2018**

Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, Minenza E, Linardou H, Burgers S, Salman P, et al. Nivolumab plus Ipilimumab in lung Cancer with a high tumor mutational burden. *Engl J Med*. 2018;378(22):2093-104.



**Herbst et al 2013**

Herbst RS, Gordon MS, Fine GD, Sosman JA, Soria JC, Hamid O, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumours [abstract 3000]. *J Clin Oncol* 2013;31(Suppl 15).

**Hirano et al 2005**

Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res* 2005;65:1089-96.

**Higgs et al 2017**

Higgs BW, Morehouse CA, Streicher K, Brohawn PZ, Steele K, Rebelatto M, et al. A baseline IFN $\gamma$  gene expression signature correlates with clinical outcomes in durvalumab-treated advanced NSCLC cancer patients. *Cancer Res* 2017;77(13 Suppl):Abstract nr 1773(Poster 1773 at AACR 2017).

**Higgs BW et al 2018**

Higgs BW et al. High tumor mutational burden (TMB) and PD-L1 have similar predictive utility in 2L+ NSCLC patients (pts) treated with anti-PD-L1 and anti-CTLA-4. *Annals of Oncology* (2018) 29 (suppl\_8): viii14-viii57. 10.1093/annonc/mdy269

**Hodi et al 2010**

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanan JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma [published erratum appears in *N Engl J Med* 2010;363:1290]. *N Engl J Med* 2010;363:711-23.

**Hodi et al 2014**

Hodi FS, Sznol M, Kluger HM, McDermott DF, Carvajal RD, Lawrence DP et al. Long-term survival of ipilimumab-naïve patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a Phase I trial [ASCO abstract 9002]. *J Clin Oncol* 2014; 32(Suppl).

**Howlander et al 2014**

Howlander N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER cancer statistics review, 1975-2011. Bethesda (MD): National Cancer Institute. Available from: URL:[http://seer.cancer.gov/csr/1975\\_2011/](http://seer.cancer.gov/csr/1975_2011/). Based on November 2013 SEER data submission (posted to the SEER web site, April 2014).

**Hui, R. et al 2017**

Hui, R. et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. *Ann. Oncol.* 28, 874–881 (2017).

**IASLC Staging Manual in Thoracic Oncology**

Goldstraw P, ed. Staging manual in thoracic oncology. 7th ed. IASLC 2010. (Available on request)

**Iwai et al 2002**

Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumour cells in the escape from host immune system and tumour immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA* 2002;99:12293-7.

**Johnson et al 2016**

Johnson DB, Frampton GM, Rioth MJ, Yusko E, Ennis R, Fabrizio D. Hybrid capture-based next-generation sequencing (HC NGS) in melanoma to identify markers of response to anti-PD-1/PD-L1. *J Clin Oncol*. 2016; 34 (suppl); abstr 105. ASCO

**Keir et al 2008**

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677-704

**E S Kim et al 2018**

E S Kim, V Velcheti, T Mekhail, T A Leal, J E Dowell, M L Tsai, C S R Dakhil, P Stella, V Shen, S Hu, S M Paul, D S Shames, E Schleifman, D A Fabrizio, C Yun, S Phan, M A Socinski; LBA55. Primary efficacy results from B-FIRST, a prospective phase II trial evaluating blood-based tumour mutational burden (bTMB) as a predictive biomarker for atezolizumab (atezo) in 1L non-small cell lung cancer (NSCLC), *Annals of Oncology*, Volume 29, Issue suppl\_8, 1 October 2018, mdy424.067

**Kirkwood et al 2010**

Kirkwood JM, Lorigan P, Hersey P, Hauschild A, Robert C, McDermott D, et al. Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. *Clin Cancer Res* 2010;16:1042-8.

**Klein et al 2007**

Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. *Stat Med* 2007;26:4505-19.

**Korn et al 2008**

Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of Phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol* 2008;26:527-34.

**Krambeck et al 2007**

Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al. Survivin and B7-H1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. *Clin Cancer Res*. 2007;13(6):1749-56.

**Lan and DeMets 1983**

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.

**NCCN 2014**

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>). Non-Small Cell Lung Cancer. Version 4.2014. Available from: URL: [www.nccn.org](http://www.nccn.org).

**Okudaira et al 2009**

Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an anti-tumour effect in a mouse pancreatic cancer model. *Int J Oncol* 2009;35:741-9.

**Pardoll 2012**

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-64.

**Paterson et al, 2011**

Paterson AM, Brown KE, Keir ME, Vanguri VK, Riella LV, Chandraker A, et al. The PD-L1:B7-1 pathway restrains diabetogenic effector T cells in vivo. *J Immunol*. 2011;187:1097-105

**Paz-Ares et al 2013**

Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2013;31:2895-902

**Peters et al 2019**

Peters S, Chul Cho B, Reinmuth N, Lee KH, Luft A, JuAhn M, et al. Tumor mutational burden (TMB) as a biomarker of survival in metastatic non-small cell lung cancer (mNSCLC): blood and tissue TMB analysis from D419AC00001, a Phase 3 study of first-line durvalumab +/- tremelimumab vs chemotherapy. *AACR 2019*

**Pisters and LeChevalier 2005**

Pisters KM, LeChevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. *J Clin Oncol* 2005;23:3270-8.

**Powles et al, 2014**

Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature*. 2014 Nov 27;515(7528):558-62.

**Reck et al 2014**

Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(Suppl 3):iii27-39.

**Reck, M. et al 2016**

Reck, M. et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med.* 375, 1823–1833 (2016).

**Ribas et al 2013**

Ribas A, Kefford R, Marshall MA, Punt CJA, Haanen JB, Marmol M, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. *J Clin Oncol* 2013;31:616-22.

**Rizvi et al 2015**

Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). *J Clin Oncol* 2015;33:Abstract 8032.

**Rizvi, N. A. et al 2015**

Rizvi, N. A. et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 348, 124–128 (2015).

**Rizvi et al 2018**

Rizvi et al. Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: D419AC00001. *Annals of Oncology* (2018) 29 (suppl\_10): x39-x43. 10.1093/annonc/mdy511

**Robbins 1993**

Robins J. Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. *Proceedings of the Biopharmaceutical Section, American Statistical Association*; 1993. p. 24-33.

**Robins and Tsiatis 1991**

Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Commun Stat Theory Methods* 1991; 20(8):2609-31

**Rooney et al 2015**

Rooney, M. S., Shukla, S. A., Wu, C. J., Getz, G. & Hacohen, N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell* 160, 48–61 (2015).

**Rosenberg et al 2016**

Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet.* 2016;387:1909-20.

**Samstein et al 2019**

Samstein R, Lee CH, Shoushtari A, Hellmann M, Shen R, Janjigian Y, Barron D, Zehir A, Jordan E, Omuro A, Kaley T, Kendall S, Motzer R, Hakimi A, Voss M, Russo P, Rosenberg J, Iyer G, Bochner B, Bajorin D, Al-Ahmadie H, Chaft J, Rudin C, Riely G, Baxi S, Ho A,

Wong R, Pfister D, Wolchok J, Barker C, Gutin P, Brennan C, Tabar V, Mellinshoff I, DeAngelis L, Ariyan C, Lee N, Tap W, Gounder M, D'Angelo S, Saltz L, Stadler Z, Scher H, Baselga J, Razavi P, Klebanoff C, Yeager R, Segal N, Ku G, DeMatteo R, Ladanyi M, Rizvi N, Berger M, Riaz N, Solit D, Chan T, Morris LGT. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nature Genetics* Vol 51, pages202–206 (2019)

**Sandler et al 2006**

Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2524-50.

**Scagliotti et al 2008**

Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-51.

**Schadendorf et al 2013**

Schadendorf D, Hodi FS, Robert C et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma [abstract 24]. Presented at European Cancer Congress 2013 (ECCO-ESMO-ESTRO); 27 September to 01 October 2013; Amsterdam, The Netherlands.

**Schiller et al 2002**

Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;10:92-8.

**Segal et al 2015**

Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. *J Clin Oncol* 2015;33:Abstract 3011.

**Stewart et al 2015**

Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res* 2015;3(9):1052-62.

**Snyder, A. et al 2014**

Snyder, A. et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N. Engl. J. Med.* 371, 2189–2199 (2014).

**Sun and Chen 2010**

Sun X, Chen C. Comparison of Finkelstein's Method with the conventional approach for interval-censored data analysis. *Stat Biopharm Res* 2010;2:97-108.

**Tarhini and Kirkwood 2008**

Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. *Expert Opin Biol Ther* 2008;8:1583-93.

**Topalian et al 2012**

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443-54.

**Topalian et al 2014**

Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*, 2014;32:1020-30.

**Vamsidhar Velcheti et al 2018**

Vamsidhar Velcheti, Edward S. Kim, Tarek Mekhail, Christopher Dakhil, Philip J. Stella, Xiaowei Shen, Sylvia Hu, Sarah M. Paul, David S. Shames, Cindy Yun, See-Chun Phan, and Mark A. Socinski *Journal of Clinical Oncology* 2018 36:15\_suppl, 12001-12001

**Weber et al 2012**

Weber J, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691-7.

**Whitehead and Whitehead 1991**

Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med* 1991;10:1665-77.

**Wolchok et al 2013**

Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013;369:122-33.

**Yuan et al 2011**

Yuan J, Adamow M, Ginsberg BA, Rasalan TS, Ritter E, Gallardo HF, et al. Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlated with clinical benefit in advanced melanoma patients treated with ipilimumab. *Proc Natl Acad Sci USA* 2011;108:16723-8.

**Zhang et al 2008**

Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Anti-tumour immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. *Cytotherapy* 2008;10:711-9.

**Zou and Chen 2008**

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol.* 2008;8(6):467-77.

## **Appendix A Additional Safety Information**

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

#### **Life threatening**

‘Life-threatening’ means that the patient 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 patient’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (e.g. hepatitis that resolved without hepatic failure).

#### **Hospitalization**

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g. bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient 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, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention to prevent 1 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 (e.g. neutropenia or anemia 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 patient 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 etiology 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.

## **A 1 Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.



A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

## **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, e.g. 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, e.g. 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    Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law**

### **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. Specific guidance on the managing liver abnormalities can be found in Sections 5.2.1 and 6.1.5 of the protocol.

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.

### **Definitions**

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

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT)  $\geq 3 \times$  Upper Limit of Normal (ULN) together with Total Bilirubin (TBL)  $\geq 2 \times$  ULN 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  $\geq 3 \times$  ULN **together with** TBL  $\geq 2 \times$  ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, or 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.

#### **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  $\geq 3 \times$  ULN
- AST  $\geq 3 \times$  ULN
- TBL  $\geq 2 \times$  ULN

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 two [Definitions](#) within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory electronic case report form (eCRF)

#### **Follow-up**

##### **Potential Hy's Law Criteria not met**

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

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

##### **Potential Hy's Law Criteria met**

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver eCRF 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

## **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 eCRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF 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 amending the reported term if an alternative explanation for the liver biochemistry elevations is determined

### **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<sup>#</sup> compared with the last visit where PHL criteria were met<sup>#</sup>
  - 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 [Potential Hy's Law Criteria met](#) of this Appendix

<sup>#</sup>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.

### **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 section "[Actions required when potential Hy's law criteria are met before and after starting study treatment](#)" of this appendix

If No: Follow the process described in Section [Potential Hy's Law Criteria met](#) of this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition<sup>#</sup> compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section **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.

## 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 D Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)**

### **Introduction**

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines ([Eisenhauer et al 2009](#)) for this study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiologic progression.

### **Definition of measurable, non-measurable, target and non-target lesions**

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least 1 measurable lesion which has not been previously irradiated.

Tumor lesions selected for screening biopsy must not be used as target lesions, unless there unless imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

### **Measurable:**

A lesion, not previously irradiated or biopsied per the protocol prior to randomization, that can be accurately measured at baseline as  $\geq 10$  mm in the longest diameter (except lymph nodes, which must have short axis<sup>1</sup>  $\geq 15$  mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements.

### **Non-measurable:**

- (i) All other lesions, including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  mm to  $< 15$  mm short axis at baseline<sup>2</sup>)

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<sup>1</sup> The short axis is defined as the longest axis perpendicular to long axis of the lymph node

<sup>2</sup> Nodes with  $< 10$  mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).



- (ii) Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI
- (iii) Tumor lesions selected for screening biopsy
- (iv) Previously irradiated lesions<sup>3</sup>
- (v) Skin lesions assessed by clinical examination
- (vi) Brain metastasis

**Special cases:**

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs)

**Target lesions:**

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline. Lymph nodes, in any location, are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ is considered as a single organ.

**Non-target lesions:**

Additional measurable and non-measurable lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

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<sup>3</sup> Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment

## Methods of assessment

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

A summary of the methods to be used for RECIST assessment is provided in [Table 1](#) below, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

**Table 1 Summary of methods of assessment**

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

CT Computed tomography; FDG-PET 18-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

### CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible images for measurement of TL assessment of NTL, and identification of any new lesions.

It is recommended that IV contrast-enhanced CT examinations of the chest and abdomen (including liver and adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to IV CT contrast, a non-contrast CT exam of the chest and an MRI with IV contrast of the abdomen (including liver and adrenal glands) is appropriate. In patients with severely compromised renal function a non-contrast CT exam of the chest and abdomen (including liver and adrenal glands) is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, and scanner across all imaging time points per patient.

### **Clinical examination**

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

### **X-ray**

#### **Chest X-ray**

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

#### **Plain X-ray**

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

### **Ultrasound**

Ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor 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.

### **Endoscopy and laparoscopy**

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

### **Tumor markers**

Tumor markers will not be used for tumor response assessments as per RECIST 1.1.

### **Cytology and histology**

Histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary for the Investigator to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive

disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

### **Isotopic bone scan**

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

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.

### **FDG-PET scan**

<sup>18</sup>F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive <sup>18</sup>F-Fluoro-deoxyglucose uptake<sup>4</sup> 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.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scans are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT examination is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan then the CT portion

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<sup>4</sup> A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed

of the PET/CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially performed.

## **Tumor response evaluation**

### **Schedule of evaluation**

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient (e.g., new lesions at follow up).

Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible and prior to the start of investigational product. Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks  $\pm$  1 week for the first 48 weeks (relative to the date of randomization; see Section 5.1 of the clinical study protocol), then every 8 weeks  $\pm$  1 week thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment/or subsequent therapy). If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the patient's scheduled visits.

For patients who discontinue study drug due to toxicity in the absence of confirmed objective progression, objective tumor assessments should be continued every 6 weeks  $\pm$  1 week for 48 weeks (relative to the date of randomization) then every 8 weeks  $\pm$  1 week until confirmed objective disease progression.

In addition to partial response and complete response, radiographic progression (PD by RECIST 1.1) requires confirmation; the confirmatory scan should occur no earlier than 4 weeks after the initial assessment of progression of disease (PD) and preferably at the next scheduled visit in the absence of clinically significant deterioration.

If progression is not confirmed then the patient should continue on study treatment and continue with imaging assessments on their regular schedule.

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

Additional assessments will be performed post confirmed objective disease progression for patients remaining on IMT treatment, retreatment, or until subsequent cancer therapy according to the clinical study protocol.

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

## **Target lesions**

### **Documentation of target lesions**

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

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

### **Special cases:**

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis
- If the CT/MRI slice thickness used is  $>5$  mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts
- If two or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion
- When a TL has had any intervention e.g., definitive radiotherapy, embolization, surgery, etc. during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form

### Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see [Table 2](#) below).

**Table 2 Evaluation of target lesions**

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

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

## Non-target lesions

### Evaluation of non-target lesions

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

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

|                        |   |
|------------------------|---|
| Complete response (CR) | Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).   |
| Non CR/Non PD          | Persistence of 1 or more NTL.   |
| Progression (PD)       | Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression <b>MUST</b> be clinically significant for the physician to consider changing (or stopping) therapy.   |
| Not evaluable (NE)     | Only relevant when 1 or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit.<br><br>Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met. |

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

To achieve “unequivocal progression” on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.



## New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of 1 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: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor 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.

## Symptomatic deterioration

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

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

## Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in [Table 4](#) below.

**Table 4 Overall visit response**

| Target lesions | Non-target lesions | New lesions | Overall response |
|----------------|--------------------|-------------|------------------|
| CR             | CR                 | No          | CR               |
| CR             | NA                 | No          | CR               |
| NA             | CR                 | No          | CR               |

**Table 4 Overall visit response**

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

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

### Confirmation of Progression

Confirmation of progression guidelines are set for the following reasons:

- For patient management and treatment decisions
- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression

Confirmed objective disease progression refers to either of the following scenarios: (1). clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or (2). in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of

progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- $\geq 20\%$  increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared with nadir
- and/or significant progression (worsening) of NTLs and/or pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point)
- and/or additional new unequivocal lesions at the confirmatory scan timepoint

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first PD by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed with imaging until confirmed objective disease progression.

## Central Review

Blinded Independent Central Review assessments are not planned for this study. However, all images will be collected, quality checked, and stored centrally by an Imaging Contract Research Organization (CRO) appointed by AstraZeneca so that the scans will be available if such verification becomes necessary. Guidelines for image acquisition, anonymization, storage at the investigative site as source data, and transfer to the Imaging CRO will be provided in a separate document. The management of patients will be based solely upon the local assessments conducted by the investigator.

If central review is conducted, the Contract Research Organization appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

## Specifications for Radiological Imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

If specified, all images will be collected, quality checked and stored centrally by the imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely upon the local assessments conducted by the Investigator.

Also if specified, further details of the Blinded Independent Central Review (BICR) will be documented in the Independent Review Charter (also referred to as the 'Imaging Charter')

## CT Scan

CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage 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. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to

the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

**b. IV contrast administration:** Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed then CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

**c. Slice thickness and reconstruction interval:** It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

## **MRI Scan**

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies e.g. neck) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

## **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 tumors: revised RECIST guideline (Version 1.1). *Eur J Cancer* 2009;45:228-47

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