AstraZeneca

Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736)
Study Code	D419AC00002
Version	9
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A Phase III Randomized, Open-Label, Multi-Center Study of Durvalumab Versus Standard of Care Platinum-Based Chemotherapy as First Line Treatment in Patients with PD-L1-High Expression Advanced Non Small-Cell Lung Cancer (NSCLC)

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VERSION HISTORY

Version 9, 18 Jun 2021
Section 1.1 Background and rationale for conducting this study and 1.1.1 Immunotherapies Reference to <<FDA>> <<US>> approval for use of durvalumab in urothelial cancer has been deleted following the voluntarily withdrawal of this conditionally approved indication by AstraZeneca, in consultation and with guidance provided by the FDA. **Section 1.4.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis and Appendix F** Inserted language describing the study conduct mitigations during study disruptions due to a health crisis. **Section 1.3.2.1 Durvalumab** Added risks for Durvalumab rash/dermatitis (pemphigoid) and immune thrombocytopenia. **Section 6.9.1 Specific toxicity management and dose modification information – Durvalumab** TMG portal was decommissioned. **Section 8 Statistical analyses by AstraZeneca** Additional analyses assessing the impact of COVID-19 may be included in the SAP. Definition of PD-L1 TC ⩾ 50% analysis set in Section 8.3.3 and OS analyses of considering the impact of switching to other immunotherapies in Section 8.5.1 were clarified. Sentence of “All data collected will be listed.” in Section 8.5 was removed. Details will be specified in SAP. Minor changes to correct typographical errors.
Version 8, 26 Feb 2020
Change the sole primary objective to dual primary objectives to compare durvalumab monotherapy versus standard of care (SoC) in terms of overall survival (OS) in all randomised patients (PD-L1 TC ≥25%) and in patients who are at low risk of early mortality (EM) based on baseline laboratory values according to a specific prognostic model. The primary objective of the study has been changed from the sole primary objective of durvalumab monotherapy versus SoC in all randomized patients (PD-L1 TC ≥25%) to the dual primary objectives of durvalumab monotherapy versus SoC in all randomised patients (PD-L1 TC ≥25%) and in patients who are at low risk of early mortality (hereafter referred to as "population at low risk

of early mortality") in terms of OS. The population at low risk of early mortality consists of patients identified by a prognostic model developed by AstraZeneca as having low risk of early mortality. The multiple testing procedure (MTP) has been updated accordingly to reflect this change.

In line with the changes to the primary objective, the analysis of interim OS will be performed when approximately 85% of final target OS events (approximately 68% maturity) in PD-L1 TC ≥25% population, approximately 85% of final target OS events (approximately 64% maturity) in the PD-L1 TC ≥25% and low risk of early mortality population, and a minimum 12 months follow-up from last patient randomized to the study (whichever occurs last). The analysis of final OS will be performed when approximately 521 death events (approximately 80% maturity) have occurred in PD-L1 TC ≥25% population and approximately 414 death events (approximately 76% maturity) in the PD-L1 TC ≥25% and low risk of early mortality population across the durvalumab monotherapy and SoC treatment groups (whichever occurs last).

All relevant sections throughout the protocol have been updated to reflect these changes. This includes the Synopsis, Section 1.2 (Rationale for study design, doses and control groups), Section 1.2.1 (Study population rationale), Section 1.2.4 (Rationale for endpoints), Section 2.1 (Primary objectives), Section 2.2 (Secondary objectives), Section 8.2 (Sample size estimate), Section 8.3 (Definitions of analysis sets) and Section 8.5 (Methods for statistical analyses).

This change has been made based on emerging data that are external to the PEARL study. Immune checkpoint inhibitors (ICIs) are profoundly changing the treatment of many types of cancer, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and Hodgkin's lymphoma, and have been associated with long-lasting tumor responses. However, an early mortality (EM) phenomenon has been observed in many randomized clinical trials comparing ICIs with active comparator arms in advanced or metastatic cancer patients, even with overall benefit ultimately favoring ICI therapy (Champiat et al 2018). While the precise etiology of this phenomenon is not clearly established, it is characterized by what seems to be disproportionately higher mortality in the early treatment period favoring the active control arm, followed by subsequent benefit in OS favoring the ICI treatment arm. This is often reflected in the clinical data by the "crossing of the Kaplan-Meier curves" suggesting a subpopulation of patients at a higher risk of EM whose advanced rate of tumor growth may initially benefit more with chemotherapy. Accordingly, it is of great therapeutic interest to better predict the risk of EM for a given patient to better choose the appropriate treatment for their individual clinical state. To aid in this objective, AstraZeneca has developed and implemented a model that predicts a patient's risk of EM to optimize the benefit: risk profile for treatment of patients with ICIs.

Changes not related to the analysis of the primary endpoint include the following:

Synopsis: Study site(s) and number of subjects planned

Slightly update the description for "global sites include China and other countries".

Remove the sensitivity analysis of PFS based on RECIST 1.1 modified for confirmation of progression using Investigator assessments in the footnote.

Section 1.1 Background and rationale for conducting this study.

A discussion added on the role of ICI in NSCLC and in 1st line setting, to reflect the evolving treatment algorithm up to date.

Section 1.3.2.1 Durvalumab

Updated the potential risk of durvalumab based on pooled safety data across the durvalumab monotherapy programme.

Section 2.2 Secondary objectives

Add PFS, ORR, DoR, APF12, PFS2 in patients with PD-L1 TC $\geqslant$ 50% as secondary endpoints, add OS, PFS, ORR, DoR, APF12, PFS2 in patients with PD-L1 TC $\geqslant$ 50% and low risk of early mortality as secondary endpoints. Remove the sensitivity analysis of PFS based on RECIST 1.1 modified for confirmation of progression using Investigator assessments in the footnote.

Section 4.1 Enrolment/screening period

Add the statement to clarify the requirement of the laboratory and imaging procedures performed prior to signing consent.

Section 6.5 Regulatory reporting requirements for SAEs

Added a new section of “Regulatory reporting requirements for SAEs” to appropriately describe the process and sponsor responsibilities for SAE and SUSAR reporting in AZ studies.

Section 6.9.2 Adverse events of special interest

Updated AESI list based on pooled safety data across the durvalumab monotherapy programme. Added more content in “Other inflammatory events”.

Section 6.10 Study governance and oversight

Updated for IDMC frequency and unblinded IDMC review on interim analysis summaries of efficacy date.

Section 7.7.1 Other concomitant treatment

Emphasis that steroids and other immunosuppressant rescue medication has to be made available to this patient population.

Section 8 Statistical analyses by AstraZeneca

Sample size estimate, definitions of analysis sets and multiple testing procedures for controlling the type I error rate were updated in alignment with revised objectives in Section 2. The sensitivity analysis of PFS based on RECIST 1.1 modified for confirmation of progression using Investigator assessments was removed in alignment with Section 2.

Additional changes are:

1. Max-combo test was added as sensitivity analysis for OS. OS subgroup analyses were modified.
2. Wording in Section 8.4.1.1 Time from randomization to second progression (PFS2) modified to clarify the timing of assessments for a second progression event, to align with the durvalumab project level CSP standard template: Actual timing of assessments for a second progression event will be according to local standard practice.
3. Wording in Section 8.4.1.1 Best objective response modified to consider 1 week assessment window instead of 3 days.
4. Wording in Sections 8.4.1.1 and 8.5 Objective response rate (ORR), duration of response (DOR) and best objective response (BOR) modified to add the analyses based on confirmed response.
5. The analysis of time to deterioration for EORTC QLQ-C30 scales/items was modified in Section 8.4.3.1. Wording in Section 8.4.3.2 Lung cancer module (EORTC QLQ-LC13) modified to consider a minimum clinical meaningful change of 10 instead of 5.
6. The analysis of expected duration of response (EDoR) was removed to be consistent with other durvalumab studies in Section 8.5.
7. The analysis of comparison of APF12, OS12, OS18 were removed to be consistent with other durvalumab studies in Section 8.5. Kaplan Meier estimates of APF12, OS12 and OS18 will still be provided for each treatment arm.

Minor changes to correct typographical errors.

Version 7, 22 May 2019

Section 4 Study plan and timing of procedures

In Tables 4, a text added to clarify that immunogenicity assessment (ADA sampling) is applicable for patients in the durvalumab group only.

Section 8 Statistical analyses by AstraZeneca

Minor changes to correct typographical errors.

Version 6, 09 Apr 2019

Synopsis was modified to reflect the changes in Section 2 (Study objectives), Section 7.2.2 (Duration of treatment), Section 8 (Statistical analyses by AstraZeneca) and Section 9.3 (Study timetable and end of study).

Section 1.2.4 Rationale for endpoints

OS18 and OS24 were added as secondary endpoints, based on emerging data external to this study suggesting the clinical importance in the immunotherapy setting.

Section 1.3 Benefit/risk and ethical assessment

Updated information from the PACIFIC study was added.
Additional information on the potential risks that based on the mechanism of action of PD-1/PD-L1/CTLA-4 anti-bodies were added.

Section 2 Study objectives

Explicitly stated that the primary endpoint for this study is the OS in PD-L1 TC ≥ 25% population for the sake of clarity.

OS18 and OS24 were added as secondary endpoints, based on emerging data external to this study suggesting the clinical importance in the immunotherapy setting.

Section 3.9 Discontinuation of investigational product

The procedures for patients who permanently discontinue drug for reasons other than objective RECIST disease progression and discontinued for unconfirmed progression was introduced in this section to align with the durvalumab project level CSP standard template and to maintain consistency across the durvalumab program.

Clarified the survival follow-up procedure for patients who decline to return to the site.

Section 3.10.2 Withdrawal of the informed consent

Specified in more detail on the different scenarios of withdrawn consent.

Specified the survival follow-up procedure for withdrawn consent and lost to follow-up patients.

Section 4 Study plan and timing of procedures

Added clarifications to the schedules for regular study assessment and in the event of dose delay.

Section 4.2 Treatment period

The recommended assessment order for vital signs, electrocardiograms (ECGs), and blood draws scheduled for the same nominal time were added, to be in line with the follow-up period.

Section 5.1 Efficacy assessments

Modified the criteria for confirmed radiologic progression to align with the durvalumab project level CSP standard template which is consistent with previous version but has wording modified.

Section 5.2.1 Laboratory safety assessments

Clarified the requirement of 'All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IP (see Table 4).

Section 5.2.4 Vital signs

Modified the vital sign assessment guidance to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 6.1.8 Death

Added the instruction to remind that all death cases with causality assessment should be documented in the 'Statement of Death page' in the eCRF.

Section 6.7 Medication Error

Section 6.7 was added to outline the medication error reporting procedure.

6.8.1 Specific toxicity management and dose modification information – Durvalumab

Slightly revised the session to indicate that the TMGs is now a standalone clinical document as annex to the protocol.

Section 6.8.2 Adverse events of special interest

Modified the AESI category and instruction on Toxicity Management Guidelines to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Updated terminology from immune-related Adverse Event (irAE) to immune-mediated Adverse Event (imAE).

Section 7.1.1 Durvalumab (MEDI4736)

The section for durvalumab was updated with the current recommendations for preparation and dose calculations.

Section 7.2.2 Duration of treatment

Wordings modified on 'Progression during treatment' based on durvalumab project level CSP standard template to be consistent across program.

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

Section 7.3 Labeling

Added the wording of 'Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.'

Section 7.4 Storage

Updated the instruction for storage, the requirement of temperature log, and the report of temperature excursions outside the permissible range.

Section 7.7 Concomitant and other treatments

Added the remind of reporting duration on concomitant medicines which should be 'from the time of screening until the end of the clinical treatment phase of the study, including the 90 days follow-up period following the last dose of study drug', to be aligned with Table 4.

Added 'For agents in the SoC arm, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.'

Section 8 Statistical analyses by AstraZeneca

Updated to be consistent with the change in Section 2 with the following other changes.

Update of interim analysis plan to remove one of two planned IA's and conduct the only IA at 85% of target OS events at final and a minimum 12 months follow-up since last patient randomized in the study (whichever occurs later) in sections 8.2, 8.4 and 8.5. Emerging data external to this study suggests that longer follow-up is needed for an IA.

Removal of disease control rate in sections 8.4.1.1 and 8.5.3. Emerging understanding of immunotherapy suggests that the existing efficacy endpoints in Section 2 are sufficient to characterize the clinical benefit.

Minor changes to correct typographical errors.

Section 9.3 Study timetable and end of study

Updated the end of study date as per the latest prediction.

Dosing Modifications and Toxicity Management

Previous Appendix F (Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion related, and Non Immune-mediated Reactions) was removed from study protocol and became a standalone clinical document.

Version 5, 13 Mar 2018

Synopsis was modified to reflect the changes in Section 1.4 (Study design), Section 2 (Study objectives) and Section 8 (Statistical analyses by AstraZeneca).

Section 1.2.4 (Rationale for endpoints)

The rationale was updated as OS will be the only primary endpoint.

Section 1.3 (Durvalumab)

Information on PACIFIC study was added.

Section 1.4 (Study Design)

Numbers of subjects randomized, and per treatment group were updated to 650 and 325, respectively. Figure 1 (overall study design) was updated accordingly. The sample size was updated based on changes of primary endpoints as well as changes of statistical assumptions.

Section 2 (Study objectives)

1. Remove PFS from co-primary endpoint and make it a secondary endpoint. This change is based on emerging data suggesting OS might be a more meaningful endpoint to demonstrate efficacy in first line NSCLC patients treated with IO.
2. The RECIST based secondary endpoints including PFS, ORR, DoR, and APF12 will be based on Investigator assessments instead of BICR assessments. Sensitivity analysis based on irRECIST 1.1 is removed.
3. To assess the efficacy of durvalumab compared to SoC in terms of OS among subjects with PD-L1 ≥ 50% is added as one of the secondary objectives.

Section 3.2 – Exclusion criteria

The following expression is added to Exclusion criterion #4 ‘Asymptomatic brain metastases discovered during screening period must confirm stability in no less than 2 weeks by imaging (intravenous contrast-enhanced MRI (preferred) or IV contrast-enhanced CT).’ Patients with brain metastases should not enter the study unless the brain metastases are asymptomatic and confirmed stable.

Exclusion criterion #7 added ‘or haemoglobin ⩾9.0 g/dL but with transfusion 4 weeks prior to the screening and randomization’.

Exclusion criterion #13 ‘Mean QT interval corrected for heart rate using Fridericia’s formula (QTcF) ⩾ 470 ms’ has been deleted. Data from the ECG analysis in ATLANTIC suggest no effect of durvalumab on QT interval, and the durvalumab serum concentration versus change in QTcF analysis did not indicate a risk for clinically significant QT prolongation. Current data did not indicate any QT liability or identify a risk for other adverse ECG or cardiovascular effects following exposure to durvalumab.

Section 3.3 – Patient enrolment and randomization

The requirement for EGFR and ALK status before sending PD-L1 sample is deleted. There are no medical or scientific concerns associated with running EGFR/ALK and PD-L1 test at the same time. Therefore, it is allowed to test EGFR/ALK/PD-L1 in parallel.

Remove the procedure to record the pre-defined SOC in IVRS/IWRS system.

Section 4 (Study plan and timing of procedures)

In Tables 2 and 4, footnotes relating to ADA collection during/after retreatment were removed as retreatment is not applied for this study.

The title of Table 4 was revised properly.

Section 5.1 (Efficacy assessments)

The original plan of full BICR review is updated to be performed at the discretion of AstraZeneca as PFS changed to secondary endpoint.

Section 5.2.3 – Electrocardiograms

Removed QTcF requirement to keep consistent with exclusion criteria.

Section 5.4.2 – Storage and destruction of ADA samples

Add the clarification for China.

Section 5.5-Biomarker analysis

Add the clarification for China.

Modify the wording on Chain of custody of biological samples based on practice.

Section 6.3.12 (Safety Data To Be Collected following the final DCO of the study)

This section was introduced to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 7.2.2 (Duration of treatment)

Post final Data Cut Off information was introduced in this section to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 8.2 (Sample size estimate)

1. PFS has been dropped from co-primary endpoints. Sample size is updated to power for primary OS analysis. The alpha previously assigned to PFS has been reassigned to OS.

2. OS assumption is revised. As a result, the number of subjects randomized increase from 440 to 650. The final OS analysis will occur after approximately 520 events have been observed. Two OS IAs are planned at approximately 60%, and 72% of target events.

Section 8.3 (Definitions of analysis sets)

Table 9 is updated to reflect the changes in Section 2.

PD-L1 TC ⩾ 50% analysis set was added.

Section 8.4 (Outcome measures for analyses)

Updated to be consistent with changes in Section 2. The efficacy variables based on BICR assessments have been removed.

Section 8.5 (Methods for statistical analyses)

Updated to be consistent with changes in Section 2 and Section 8.2 with following additional changes:

1. Adding the subgroup analyses for OS endpoint (including but not limited to, sex, age at randomization, level of PD-L1 expression, histology and smoking status, and region) and some supportive analyses (access the effect of covariates on HR, test the interaction between treatment and stratification factors).

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3. Test of secondary OS endpoint is included in the multiple testing procedure.

Appendix D (Guidelines for Evaluation of Objective Tumor Response)

Central review section is removed.

Version 4, 15 December 2017

Section Protocol synopsis and 8.5.1.1 -Progression-free survival

Typo update: The HR will be estimated using a stratified Cox model.

Section Protocol synopsis

Progression during treatment some wordings are updated to be in line with the new protocol template.

Section 1.1.1 – Immunotherapies, 1.1.2 – Durvalumab, 1.2.2 – Durvalumab dose rationale and 1.3.2.1 – Potential risks

Background information, durvalumab PK/PD data, clinical data and safety profile have been updated according to the new investigator's brochure.

Section 3.1 – Inclusion criteria

The performance status criteria used in criterion #6 has been updated as 'World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG)' to ensure accuracy of expression.

Life expectancy of at least 12 weeks has been added as inclusion criterion #8.

Section 3.2 – Exclusion criteria

Some more exceptions are added to original exclusion criterion #14 regarding autoimmune and inflammatory disorders.

Section 3.8 – Restrictions, section 3.9 – Discontinuation of investigational product

Some wordings are updated to be in line with the new protocol template.

Section 5.3.3 – ECOG performance status

Added "5 = Dead"

Section 5.3.4 – Pneumonitis (ILD) investigation

The whole section has been added to instruct investigation of pneumonitis and to support the use of ILD module in eCRF.

Section 6.1.8 – Deaths

An instruction about the recording of deaths occurring after defined safety follow up period has been added.

Section 6.3 – Recoding of adverse events, section 6.5 - overdose

The wordings have been updated based on Durvalumab project level CSP standard template to be consistent across program.

Section 6.7.1 - Specific toxicity management and dose modification information – Durvalumab

An overall irAE management and dose modification principles has been added. the etiology of adverse events should be carefully investigated and durvalumab Dosing Modification and Toxicity Management Guidelines should be referred to if AE is considered potentially immune related. Dose reductions of Durvalumab is not permitted.

Section 6.7.2 - Durvalumab adverse events of special interest

AESI list has been updated. Myocarditis and myositis/polymyositis have been added to the list to reflect the update of durvalumab safety profile. Some minor changes of description have been made to other AESIs.

Section 6.7.3 - Standard of Care agents

The wordings have been updated based on Durvalumab project level CSP standard template to be consistent across program.

Section 7.2.1 – Treatment regimens

Clarified that durvalumab treatment should be given unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Clarified the standard infusion time is one hour. SoC regimen in CSP should be strictly followed once chosen unless local standard clinical practice guideline or local prescribing information states otherwise.

Section 7.2.2 – Duration of treatment

The definition of duration of treatment and progression during treatment is updated. Both arms will continue therapy until disease progression. Both arms with PD can receive treatment beyond PD if they continue to receive benefit from their assigned treatment and meet the criteria for treatment in the setting of PD. Wordings have been updated based on Durvalumab project level CSP standard template to be consistent across program.

Section 7.7 – Concomitant and other treatments

Emphasised that patients should consult the investigator before taking any medications.

Restricted, prohibited, and permitted concomitant medications list has been updated. The usage of immunosuppressive medications has been revised to give a more specific instruction. EGFR TKIs and herbal remedies have been added as prohibited medication. Inactivated viruses have been added as permitted medication.

Section 7.7.2 – Durvalumab drug drug interactions

Standard wordings of drug interactions has been added based on Durvalumab project level CSP standard template to be consistent across program.

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

The new version of Dose Modification and Toxicity Management Guidelines have been added to replace the old one.

Version 3, 19 September 2016

Title pages and Section 7 – Investigational product and other treatments

MEDI4736 is replaced with its generic name "durvalumab" in the study title and throughout the document.

In Section 7, "durvalumab (MEDI4736)" is used to clarify that durvalumab and MEDI4736 are the same drug and the names may be used interchangeably in other study documents and drug labels.

"Asia Pacific" is removed due to the planned participation of other countries outside of Asia in order to recruit approximately 10% Caucasian patients. The inclusion of 10% Caucasian patients is to provide evidence for durvalumab monotherapy in support of the global program.

Synopsis, Section 1.2.4 – Rationale for Endpoints, Section 2 – Study Objectives, Section 5.1 – Efficacy Assessments, Section 8.4 – Outcome Measures for Analysis, Section 8.5 – Methods for Statistical Analysis

The primary and secondary objective endpoints have been updated to reflect changes to endpoint measures - Blinded Independent Central Review (BICR) tumor assessments rather than Investigator assessments. Investigator assessments will be used for sensitivity analysis. This change was made in order to comply with China regulatory requirement for assessments to be based on BICR if PFS will be used for registration.

Synopsis, Section 1 – Introduction, Section 1.4 – Study design, Section 2, and Section 3 – Study objectives, Section 3 – Patient selection, section 7-IP and other treatment and Section 8 – Statistical Analyses

The overall study design was revised from a 3-arm study of combination therapy of durvalumab + tremelimumab vs durvalumab vs SoC to 2-arm study of durvalumab monotherapy vs SoC.

The assessment of progression-free survival (PFS) and overall survival (OS) were nominated as co-primary objectives. Primary and secondary objectives, endpoints and rational for endpoints were modified accordingly.

Study population was updated to include only PD-L1-high patients (as PD-L1 expression ≥ 25% who shall be randomized on a 1:1 ratio into 2 treatment groups: durvalumab and SOC.

The sponsor decided to amend the clinical development strategy of durvalumab to: a) allow evaluating the efficacy of durvalumab monotherapy comparing with SoC with sufficient power in a 2-arm study; b)refine the target patient population from PD-L1 unselected to PD-L1 high expression that has greater possibility to respond to durvalumab in order to improve the benefit risk profile of the study; c) accommodate the emerging data from other immuno-oncology studies, which suggest that the treatment benefit of immunotherapies can more strongly manifest in OS compared to PFS, this enables to increase the possibility of success of the study and also in line with the consultation with Chinese Health Authority.

Introduction was updated to remove irrelevant references to the combination treatment or tremelimumab.

Stratification factors were amended to include level of PD-L1 expression and histology + smoking status. Smoking status was added based on results in CD-ON-MEDI4736-1108 study showing difference response rates based on smoking status. Level of PD-L1 expression was added to ensure the uniform distribution of PD-L1 intensity which correlates with the magnitude of response in each treatment group.

Inclusion and exclusion criteria were updated to add patient must have tumor cell PD-L1-high expression status, prior to randomization, defined as ≥ 25% PD-L1 ‑ membrane expression in tumoral tissue. The requirement for patients to use effective birth control for up to 180 days after last dose of IP was also removed since only up to 90 days is required for durvalumab.

Statistical analysis plan was updated accordingly based on study design change.

Synopsis, Section 1.4 – Study design and Section 8.2 – Sample size estimate

Numbers of subjects enrolled, randomized, and per treatment group were updated to 1760, 440, and 220, respectively. Figure 1 (overall study design) and Figure 2 (study flow chart) were updated accordingly. The sample size was updated based on statistical assumptions related to change in primary endpoints and target population.

Synopsis, Section 7.2.2 - Duration of treatment

All references to retreatment were removed since retreatment was only applicable to the durvalumab + tremelimumab treatment group in the previous CSP version. Figure 2 (study flow chart) was also updated accordingly.

Section 3 - Patient Selection, enrolment, and randomization

The following statement was deleted: “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” The prevalence rate of KRAS mutation is relatively rare in Asian population, nevertheless, EGFR mutation rate in Asia in squamous NSCLC is around 14% which is much higher than in Caucasians, permission of skipping EGFR/ALK testing in squamous patients will increase the false negative rate of EGFR/ALK testing and make the target population less homogenous.

Section 3.3- Patient Enrolment and Randomization, Section 4 – Study Plan and Timing of Procedures

In order to manage high screen failure rate due to PD-L1 expression < 25%, guidance was added to consent patient and test for PD-L1 status and EGFR and ALK status, if unknown, if clinically feasible before proceeding with the rest of the screening procedures.

Section 7.7 – Concomitant and other treatments

Updates were made including the deletion of drugs with laxative properties, herbal or natural remedies, and sunitinib from the prohibited medication table. The restrictions on these drugs are related only to tremelimumab.

Prohibiting the use mAbs against CTLA-4, PD-1, or PD-L1 within 90 days of last dose of IP was also deleted. This is in accordance with the Sponsor's new standard template for durvalumab studies since physicians and patients are at liberty to select any treatment after they discontinue the IP.

Section 3.8 Restrictions

Spermicide was removed from Table 1. Highly effective methods of contraception, it is not solely a highly effective method of contraception.

Section 6 – Safety reporting and medical management and Appendix F.

Updated toxicity management guidelines were incorporated.

Section 5.1 – Efficacy assessments, Section 7.2 – Duration of treatment, Table 4, and Appendix D.

Specified additional criteria for confirmed radiologic progression in section 5.1 and Appendix D. The CSP was also revised to clarify that confirmatory scan is required in both treatment arms provided the patient is clinically stable.

Table 4 was updated to add footnote "If the patient continues to derive benefit from study treatment, then scans should continue to be collected following the original schedule and analysed by RECIST1.1, even after confirmed radiographic progression."

Clarified criteria for treatment in setting of PD in section 7.2.2.

Section 5.5.2 – CCI [redacted]

CCI [redacted]

Version 2, 20 April 2016

Title pages

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

Title updated to specify patients from Asia Pacific rather than "Asian" patients, in anticipation that Australia may be selected to participate in the study.

Protocol Synopsis

Updated to add the information on International Coordinating Investigator Professor Yilong Wu.

Synopsis, Section 7.2.2 Duration of treatment and criteria for retreatment

Duration of treatment was modified so that patients in all groups can continue therapy until disease progression rather than stopping at 12 months. Emerging data from ongoing MEDI4736 studies is suggestive of some patients losing clinical benefit after they complete the 12 months of therapy.

In all groups, 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, and if progression events occurred in the target lesions while the patient was receiving immunotherapy during the same treatment period.

Sections 1.2.1 and 1.2.3 - MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy dose rationale

Reference made to current IB for further details on safety profile of studies D4190C00006 and CD-ON-MEDI4736-1108.

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 1.3.2.1 - MEDI4736 + tremelimumab

Pneumonitis, colitis, diarrhoea, and AST and ALT elevations were added as "identified risks". The potential risks, based on the mechanism of action of MEDI4736 and related molecules, are updated to "hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk. Other inflammatory responses with potential immune-mediated aetiology reported with MEDI4736 and similar molecules include myocarditis, pericarditis, and uveitis" in accordance with the current Investigator Brochure. A sentence was added to refer to current IB for further details on the safety profile of MEDI4736 as monotherapy or combination therapy.

Section 1.4 – Study design

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

Section 3.1 – Inclusion criteria

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 S7681 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).

This inclusion criterion was updated to clarify that testing for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) can occur locally or centrally. "Activating EGFR mutation" was changed to "sensitizing EGFR mutation" to align with global MYSTIC study.

Section 3.2 - Exclusion criteria

- 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.
- Tuberculosis (clinical evaluation) has been added to hepatitis B, hepatitis C and human immunodeficiency virus as part of the active infection exclusion criterion. The exclusion criterion Known history of clinical diagnosis of tuberculosis has been deleted. In addition 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).
- Calculated creatinine clearance >50 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24 hour urine collection
- Known allergy to other humanized mAbs was added based on comments from EMA in the review of the global MYSTIC protocol.

Section 3.3 – Patient enrolment and randomization and Study Plan Tables

- Item 3 was updated to add below paragraph to provide more clarity on EGFR and ALK mutation testing:
- 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 be used firstly for (local or central) EGFR and ALK mutation testing in accordance to inclusion criterion 4. If local laboratory will perform the test, a well-validated, local regulatory-approved kit must be used.
- To provide more clarity the study plan tables were updated to include EGFR and ALK testing as optional for patient with unknown status of ALK and/or EGFR NSCLC (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).

Exploratory Objectives and Endpoints, Section 2.4, Study Plan Tables, and Section 5 Study Assessments

- For protocol simplification, consistency with amendment in global studies, and operational feasibility CCI [redacted]
- CCI [redacted]
- The protocol was further clarified in its references to genetic sampling, optional consent, and pharmacokinetics (PK). There will be a separate PK study in Chinese patients therefore blood samples for determination of MEDI4736 and tremelimumab concentration will not be collected while samples to measure the presence of ADA in serum will be collected. There will be no optional pharmacogenetics samples collected CCI [redacted]

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 (or male condoms in countries where spermicides are not approved).
- Male patients with a female partner of childbearing potential must use a male condom plus spermicide (or male condoms in countries where spermicides are not approved), and it is highly recommended for the female partner of a male patient to also use a highly effective method of contraception.

Section 3.9 - Discontinuation of IP

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

Section 4 – Study plan and timing of procedures

- The window for Cycle 1 was amended from +1 to +3 days.
- Coagulation assessments were updated to specify that: Activated partial thromboplastin time (APTT) and international normalized ratio (INR) assessments will be performed as clinically indicated and at Screening.
- Table 4 footnote added for the ability to collect post-discontinuation tumor assessments for additional analyses: "For patients who discontinue their assigned IP following confirmed

progression, available readings of CT/MRI from local practice will be collected from the patients' medical charts while information on subsequent anticancer treatment and/or PFS2 is collected".

- Tumor evaluations were updated to add a window period: "Every 6 weeks ± 1 week for the first 48 weeks relative to the date of randomization, and then every 8 weeks ± 1 week thereafter.
- Schedule of pregnancy tests were updated from "as clinically indicated" to be performed at screening and subsequent visits during MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy treatment and retreatment periods. This change was based on comments from EMA in the review of global MYSTIC protocol.
- A footer was inserted in Table 4 to clarify that ADA sample collection is not required for patients who are in follow-up after retreatment

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.

Section 5.1 Efficacy assessments and Study Plan Tables

Sections were updated to clarify when confirmatory scans must occur (preferably at the next scheduled visit). The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression and preferably at the next scheduled visit (in the absence of clinically significant deterioration).

Section 5.2.1 - Laboratory safety assessments

In Table 5, provision is made that if the amylase and lipase analyses could not be performed in a local laboratory, then 1 or the other would be performed in line with local practice.

In Table 6, coagulation was updated to specify that APTT and INR will be assessed at Screening as indicated in the table footnote.

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.

An update was also made so that on subsequent infusion days after first infusion, patients in the MEDI4736 + tremelimumab and MEDI4736 monotherapy treatment groups will be monitored at the start of the infusion and then per institution standard and as clinically indicated.

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

Appendices and Section 6.7 – Management of investigational product-related toxicities

Appendices were updated with the addition of Appendix F which contains 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. The old version formerly inserted as Table 8 in the main body of the protocol was deleted. A new version of EORTC QLQ-C30 was included in Appendix E.

Section 6.7.1 - MEDI4736 + tremelimumab and MEDI4736 monotherapy adverse events of special interest (AESI)

This section 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.

Sections 7.2.1 Treatment regimes

The paragraph was amended to delete the part stating that for SoC therapies, a particular treatment will not be used in patients who have previously received that treatment for advanced or metastatic disease. This change is based on comments from EMA during the review of global MYSTIC protocol.

Sections 7.1.1 and 7.1.2. – MEDI4736 and tremelimumab

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

Section 7.7 – Concomitant and other treatments

In the section on prohibited medications, the following amends are made:

Systematic corticosteroid will be permitted for the prevention of chemotherapy-related toxicities (nausea/vomiting prevention and prophylaxis).

Drugs with laxative properties should be used with caution rather than avoided during treatment with and for 90 days after last dose of tremelimumab during the study.

Sunitinib should not be given within 3 months of a dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib).

Herbal and natural remedies in general, rather than those for constipation only, should be avoided during treatment with and for 90 days after the last dose of tremelimumab during the study.

Version 1, 12 June 2015

Initial creation.

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

PROTOCOL SYNOPSIS

A Phase III Randomized, Open-Label, Multi-Center Study of Durvalumab Versus Standard of Care Platinum-Based Chemotherapy as First Line Treatment in Patients with PD-L1-High Expression Advanced Non Small-Cell Lung Cancer (NSCLC)

International Co-ordinating Investigator

PPD

PPD

Guangzhou, Guangdong 510080 China

Study site(s) and number of subjects planned

The study will randomize approximately 650 patients who will receive durvalumab or platinum-based Standard of Care (SoC) therapy (325 in each group). Randomized patients must have PD-L1 high expression as defined by ≥ 25% PD-L1–membrane expression in tumoral tissue by the Ventana SP263 PD-L1 Immunohistochemistry (IHC) assay. The study will be conducted at selected global sites that include China and other countries.

Study period		Phase of development
Estimated date of first subject enrolled	Q1 2017	III
Estimated date of last subject completed	Q1 2021	III

Study design

This is a randomized, open-label, multi-center Phase III study to determine the efficacy and safety of durvalumab versus platinum-based SoC chemotherapy in the first-line treatment of advanced NSCLC in patients who are epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type and with programmed cell death ligand 1 (PD-L1) high expression.

Patients will provide a tumor tissue sample at screening to determine PD-L1 expression status (defined by Ventana SP263 PD-L1 IHC assay in which ≥25% PD-L1 membrane expression in tumoral tissue is considered high expression). **Only patients determined to have PD-L1-high expression are eligible for the study.**

Patients will be randomized in a 1:1 ratio to 2 treatment arms (durvalumab or SOC therapy) in a stratified manner according to level of PD-L1 expression (25-49% versus ≥50%), histology, and smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current smoker).

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).

Objectives

Primary Objectives:	**Outcome Measures:**
To assess the efficacy of durvalumab compared to SoC in patients with PD-L1 TC ⩾ 25% (all randomized patients)	OS
To assess the efficacy of durvalumab compared to SoC in patients with PD-L1 TC ⩾ 25% and low risk of early mortality[a]	OS

Secondary Objectives:	**Outcome Measures:**
To assess the efficacy of durvalumab compared to SoC in terms of OS	OS in patients with • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality
To further assess the efficacy of durvalumab compared to SoC in terms of PFS, ORR, DoR, OS18, OS24, APF12, and PFS2	PFS, ORR, DoR, APF12 using Investigator assessments according to RECIST 1.1, PFS2 using local standard clinical practice, OS18 and OS24 respectively in patients with • PD-L1 TC ⩾ 25% • PD-L1 TC ⩾ 25% and low risk of early mortality • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality
To assess disease-related symptoms and HRQoL in patients treated with durvalumab compared to SoC using the EORTC QLQ-C30 v3 and the LC13 module	EORTC QLQ-C30, EORTC QLQ-LC13, and changes in Eastern Cooperative Oncology Group (ECOG) performance status in patients with • PD-L1 TC ⩾ 25% • PD-L1 TC ⩾ 25% and low risk of early mortality
To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab in patients with • PD-L1 TC ⩾ 25% • PD-L1 TC ⩾ 25% and low risk of early mortality

a. The population at low risk of early mortality consists of patients identified by a prognostic model developed by AstraZeneca as having low risk of early mortality.

Safety Objective:	**Outcome Measures:**
To assess the safety and tolerability profile of durvalumab compared to SoC	AEs, physical examinations, laboratory findings, and vital signs

Target subject population

Adult patients (age≥18 years) with histologically or cytologically confirmed advanced (stage IV) NSCLC who are treatment naive, EGFR and ALK wild type, and with PD-L1-high expression.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients in durvalumab group will continue therapy until disease progression, or unacceptable toxicity whichever occurs first. Patients in the SoC group will continue up to disease progression (in general up to 6 cycles of treatment plus maintenance if eligible).

Progression during treatment

During the treatment period patients in both arms may continue receiving therapy in the setting of unconfirmed radiologic progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), at the Investigator's discretion, until progression is confirmed. A confirmatory scan is required following a RECIST 1.1 overall 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 both arms with PD by 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 arm 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 treatment period.

Follow up of patients post discontinuation of study drug

Patients who have discontinued study 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 randomised in the study will be followed up for survival.

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the scheduled DCO for final analysis and final database lock may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the scheduled DCO for final analysis, it is recommended that the patients continue the scheduled site visits.

Investigators should continue to monitor and document data for all study patients in the source notes after scheduled DCO for final analysis and final database lock. Dependent on the analysis results, a decision may be made to continue further data collection for a longer period with intent to analyse long-term OS and safety data to fulfil any other potential Health Authority requirements. Any additional long-term analysis may be further clarified through addendum to main statistical analysis plan, which will be developed before DCO for the long-term analysis. Data will be collected until any of following conditions are met:

- Until remaining patients in the study (including patients after discontinuation of study treatment) have discontinued the study *OR*
- Remaining patients have been transferred into a roll-over study *OR*
- If the sponsor decides to stop data collection, patients ongoing study treatment at this time and deriving clinical benefit from their assigned treatment will be allowed to continue treatment and only SAEs will be collected.

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 PEARL and evaluated as a combined dataset.

Investigational product, and mode of administration

Durvalumab (MEDI4736)

- Durvalumab (MEDI4736) 20 mg/kg via IV infusion Q4W, starting on Week 0

Standard of Care therapy

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

- Paclitaxel + carboplatin: Paclitaxel 175 mg/m^2 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.
- Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m^2 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^2 via IV infusion on Days 1 and 8 of each 21-day cycle + 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.
- Pemetrexed + cisplatin (non-squamous patients only): Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 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^2 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 durvalumab compared with SoC in terms of overall survival (OS) in advanced NSCLC patients with EGFR and ALK wild-type and PD-L1-high expression (TC ≥ 25%) tumors, and in the PD-L1 TC ≥ 25% and low risk of early mortality population. OS will be defined as the time from the date of randomization until death by any cause. To strongly control for type I error at a 5% level (2 sided), an alpha of 4% (2 sided) will be used for the OS comparison of durvalumab versus SoC in the PD-L1 TC ≥ 25% population, and an alpha of 1% (2 sided) will be used for the OS comparison of durvalumab versus SoC in the PD-L1 TC ≥ 25% and low risk of early mortality population. The study will be considered to have met its primary objective if any of the dual primary OS results are statistically significant.

Secondary efficacy variables include OS in patients with PD-L1 TC ≥ 50%, and OS in patients with PD-L1 TC ≥ 50% and low risk of early mortality, as well as progression free survival (PFS), objective response rate (ORR), duration of response (DoR), 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) in patients with PD-L1 TC ≥ 25%, PD-L1 TC ≥ 25% and low risk of early mortality, PD-L1 TC ≥ 50%, and PD-L1 TC ≥ 50% and low risk of early mortality. All tumor-assessment-related endpoints are as assessed by Investigators.

Efficacy data will be summarized and analyzed using 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 study treatment are included in the ITT population.

Approximately 650 patients will be randomized 1:1 to durvalumab or SoC. The randomization will be stratified based on level of PD-L1 expression (25-49% versus ≥50%), histology and smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current smoker). The final (primary) analysis of OS will be performed when all of the following conditions have been met.

- approximately 521 OS events (approximately 80% maturity) have occurred across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% population
  And
- approximately 414 OS events (approximately 76% maturity) have occurred across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% and low risk of early mortality population.

One interim analysis to assess the superiority of the durvalumab group (compared to SoC group) in terms of OS will be performed when all of the following conditions have been met

- approximately 85% of the target 521 OS events (approximately 68% maturity) have been achieved across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% population
  And
- approximately 85% of the target 414 OS events (approximately 64% maturity) have been achieved across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% and low risk of early mortality population
  And
- a minimum 12 months follow-up from last patient randomized to the study.

Durvalumab versus SoC (OS in the PD-L1 TC ≥ 25% population)

With an estimated 521 OS events, the trial will have approximately 86% power to demonstrate statistical significance at the 2-sided alpha level of 3.334% (with overall alpha for OS 4%) for the comparison of durvalumab versus SoC, allowing for 1 interim analysis conducted at approximately 85% of the target events. The alpha level will be controlled by using the Lan and Demets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach.

Durvalumab versus SoC (OS in the PD-L1 TC ≥ 25% and low risk of early mortality population)

With an estimated 414 OS events, the trial will have approximately 87% power to demonstrate statistical significance at the 2-sided alpha level of 0.862% (with overall alpha for OS 1%) for the comparison of durvalumab versus SoC, allowing for 1 interim analysis conducted at approximately 85% of the target events.

The primary OS will be analyzed using a stratified log-rank test. The effect of treatment will be summarized by the HR estimated from a stratified Cox model with corresponding 95% confidence interval (CI) and p-value.

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

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{ss}	Area under the curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
CD	Cluster of differentiation
CI	Confidence interval
$C_{max,ss}$	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
$C_{trough,ss}$	Trough plasma concentration at steady state
CCI	[redacted]
DCR	Disease control rate
DCO	Data Cut Off
DLT	Dose-limiting toxicity
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EM	Early mortality
EORTC	European Organisation for Research and Treatment of Cancer
CCI	[redacted]
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Fluorouracil
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICI	Immune checkpoint inhibitors
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMT	Immunomodulatory therapy
IP	Investigational product
imAE	Immune-mediated adverse event
irRECIST	Immune-related RECIST criteria
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

Abbreviation or special term	Explanation
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NLR	Neutrophil to lymphocyte ratio
NSCLC	Non–small-cell lung cancer
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-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Progression-free survival after subsequent anticancer therapy
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
Q8W	Every 8 weeks
QLQ-C30 v3	30-item core quality of life questionnaire, version 3
QLQ-LC13	13-item lung cancer quality of life questionnaire
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RCC	Renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TKI	Tyrosine-kinase inhibitor
TMGs	Toxicity management guidelines
TSH	Thyroid-stimulating hormone
UC	Urothelial carcinoma
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 globally (19.4% of the total cancer deaths; Gandhi et al 2018

Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, DeAngelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078-92.

GLOBOCAN 2012). The incidence rate of lung cancer in China is relatively higher and also increasing with a more rapid rate than in western countries (Chen, et al 2014). Non-small-cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. At the time of diagnosis approximately 70% of patients with NSCLC already have advanced disease not amenable to surgical resection. Furthermore, a significant percentage of patients with early stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005).

Despite advances in the diagnosis, imaging, staging, and treatment of NSCLC, the estimated overall 5-year survival for patients with Stage IV NSCLC on a global scale remains to be low; 11% and 17% in Europe and US respectively (D'Addario et al 2010, Howlander et al 2014). In China, the 5-year survival is less than 20% (Zhou 2014). Patients presenting with advanced NSCLC demonstrate different biological behavior and lead to different survival outcome depending on the presence or absence of targetable oncogenes (i.e. EGFR sensitizing mutation or ALK translocation). Presence of an EGFR sensitizing mutation or ALK translocation is often associated with a longer survival of around 24 to 36 months following the introduction of targeted treatments for these genetic alterations. On the contrary NSCLC with Wild type EGFR and ALK status usually correlates with poor prognosis (overall survival: 12 months or even less). Standard of care treatment is with platinum-based chemotherapy. (Fukuoka et al 2011). Up to 30% patients may respond to the 1st line chemotherapy, nevertheless the durations of responses (DoR) are limited and toxicities can be a major limiting factor, which indicates a high unmet medical need in this population. 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 (Chen, et al 2014, Ciuleanu et al 2009, Paz-Ares et al 2013).

Common first-line treatment regimens for advanced NSCLC are typically platinum-based doublets including 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. The

selection of a specific regimen is often dictated by local practice and individualized on a case-by-case basis. In addition to systemic chemotherapy, single-agent immunotherapy and combination therapy of immunotherapy with chemotherapy are approved for the first-line treatment of metastatic NSCLC. Despite combination therapy demonstrating an improvement in OS and progression free survival (PFS) versus SoC chemotherapy alone, certain subgroups of patients may not tolerate the combination of immunotherapy and chemotherapy (Gandhi et al 2018). Therefore, there is still a significant unmet medical need for additional treatment options for use in this patient population.

Immune checkpoint inhibitors (ICIs) have demonstrated success as treatment across multiple tumor types. Together, programmed cell death 1 (PD-1) and PD-L1 antibodies (e.g., pembrolizumab, nivolumab, and atezolizumab) have been approved in various regions for the treatment of multiple oncology indications including malignant melanoma, NSCLC, renal cell carcinoma (RCC), UC, head and neck squamous cell carcinoma (HNSCC), and Hodgkin's lymphoma. Durvalumab, an anti-PD-L1 antibody, has been approved to treat locally advanced or metastatic urothelial carcinoma, unresectable stage III non-small cell lung cancer, and extensive-stage small cell lung cancer (administered in combination with chemotherapy). Refer to the package insert (or label) for your specific country, as applicable. Approval in NSCLC was based on results from the PACIFIC study (see section 1.3.1.1).

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 part of a complex system of receptors and ligands that are involved in controlling T-cell activation. Programmed cell death 1 (PD-1) receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7 H1; CD274) and PD-L2 (B7 DC; CD273) (Okazaki and Honjo 2007). The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

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.

PD-L1 is expressed in a broad range 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 addition, high mutational burden e.g. in bladder carcinoma (Alexandrov et al, 2013) may contribute to the responses seen with immune therapy.

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 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-L1class showing clinical activity in a wide range of tumor types.

1.1.2 Durvalumab

Durvalumab 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.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored The primary OS will be analyzed using proliferation of IFN-γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab 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 durvalumab are summarized in Section 1.3.1.1 and 6.9.2. Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics; see Section 6.9 for guidance on management of durvalumab-related toxicities.

1.1.3 Rationale for conducting this study

Current therapies for advanced NSCLC with EGFR and ALK wild type have poor outcomes, with responses to systemic chemotherapy in the first-line setting of up to 30% (Pirker et al 2013), and a median OS of approximately 10 to 12 months (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 (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 an antibody that blocks the interaction between PD-L1 and its receptors, durvalumab may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile. (Brahmer et al, 2012, Topalian et al 2012) Higher responses have been observed in patients with PD-L1-positive tumors than patients with PD-L1-negative tumors. In addition, durvalumab has shown durable responses in NSCLC in Study 1108 (see Section 1.3.1.1).

Based on the preliminary clinical efficacy and safety data observed in patients with NSCLC in Study 1108, AstraZeneca plans to determine the activity of durvalumab as first-line treatment in patients with NSCLC. The preliminary efficacy, safety, and tolerability data of durvalumab in Study 1108 support the development of these treatments in NSCLC. The primary objectives of this study are to assess the efficacy of durvalumab compared with standard of care (SoC) in terms of overall survival (OS) in advanced NSCLC patients with EGFR and ALK wild-type

and PD-L1-high expression (TC ≥ 25%) tumors, and in the PD-L1 TC ≥ 25% and low risk of early mortality population.

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 Study population rationale

1.2.1.1 Rationale for selecting patients with PD-L1-high expression status

Efficacy data of durvalumab in study 1108 in front line NSCLC cohort (N=59) published in ASCO 2016 (Antonia et al 2016) indicated an ORR of 29% and DCR of 41% with a minimum of 24 weeks follow up period in PD-L1-high expression population, defined as ≥ 25% tumor cells staining for PD-L1 at any intensity. One patient had complete response. The ORR was lower in PD-L1 low/neg population defining as < 25% tumor cells staining for PD-L1 at any intensity, in which only one patient responded to the treatment among 11 patients. The findings indicated PD-L1 positivity status correlated with clinical activity of durvalumab and should be prospectively identified in the protocol to select patients who are more likely to derive clinical benefit from durvalumab.

1.2.1.2 Rationale for selecting patients who are most appropriate for treatment with durvalumab monotherapy

Immune checkpoint inhibitors (ICIs) are profoundly changing the treatment of many types of cancer, including melanoma, NSCLC, renal cell carcinoma (RCC), SCCHN, urothelial carcinoma (UC), and Hodgkin's lymphoma, and have been associated with long-lasting tumor responses. However, an early mortality (EM) phenomenon has been observed in many randomized clinical trials comparing ICIs with active comparator arms in advanced or metastatic cancer patients, even with overall benefit ultimately favoring ICI therapy (Champiat et al 2018). While the precise etiology of this phenomenon is not clearly established, it is characterized by what seems to be disproportionately higher mortality in the early treatment period favoring the active control arm, followed by subsequent benefit in OS favoring the ICI treatment arm. This is often reflected in the clinical data by the "crossing of the Kaplan-Meier curves" suggesting a subpopulation of patients at a higher risk of EM whose advanced rate of tumor growth may initially benefit more with chemotherapy. Accordingly, it is of great therapeutic interest to better predict the risk of early mortality for a given patient to better choose the appropriate treatment for their individual clinical state. To aid in this objective, AstraZeneca has developed and implemented a model that predicts a patient's risk of early mortality to optimize the benefit:risk profile for treatment of patients with ICIs. CCI [redacted] The model produces a score representing the probability of death occurring in ⩽ 12 weeks for each patient. The model is then converted to a status that assigns patients to prognostic categories of high or low risk. Patients

with a score above the cut-off are identified as high risk of EM, and patients at or below the cut-off are identified as low risk of EM.

1.2.2 Durvalumab dose rationale

A durvalumab dose of CCI is supported by *in vitro* data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from CCI durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at CCI, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses CCI is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

A population PK model was developed using the data from Study 1108 (CCI (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both CCI regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with CCI and median $Ctrough_{,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the CCI dosing regimen is anticipated to be consistent with CCI with the proposed similar dose of CCI expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the CCI regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of CCI

Clinical data

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the CCI regimen.

1.2.3 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 the first-line treatment 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 NSCLC and allow sufficient flexibility for Investigators and patients to select the agents that reflect their normal clinical practice and national guidelines (NCCN 2014, Reck et al 2014).

1.2.4 Rationale for endpoints

The primary objectives of this study are to assess the efficacy of durvalumab compared with standard of care (SoC) in terms of overall survival (OS) in advanced NSCLC patients with EGFR and ALK wild-type and PD-L1-high expression (TC $\geq$ 25%) tumors, and in the PD-L1 TC $\geq$ 25% and low risk of early mortality population.

Emerging data in immuno-oncology suggest that the treatment benefit of immunotherapies can more strongly manifest in OS compared to PFS (Brahmer et al 2015, Fehrenbacher et al 2016), and therefore, OS is determined as the primary endpoint.

The secondary efficacy endpoints of OS (assessed separately in PD-L1 TC $\geq$ 50% population, and PD-L1 TC $\geq$ 50% and low risk of early mortality population), PFS, ORR, DoR, proportion of patients alive and progression-free at 12 months from randomization (APF12), and time to second progression (PFS2), proportion of patients alive at 18 months from randomization (OS18), proportion of patients alive at 24 months from randomization (OS24) (assessed separately in the PD-L1 TC $\geq$ 25% population, PD-L1 TC $\geq$ 25% and low risk of early mortality population, PD-L1 TC $\geq$ 50% population, PD-L1 TC $\geq$ 50% and low risk of early mortality population) will be investigated to further evaluate the anti-tumor effect of durvalumab compared to SoC. PFS, ORR, DoR, and APF12 will be assessed using investigator assessments according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).

The secondary health-related quality of life (HRQoL) assessments (the European Organisation for Research and Treatment of Cancer [EORTC] 30-item core quality of life questionnaire, version 3 [QLQ-C30 v3] and 13-item lung cancer quality of life questionnaire [QLQ-LC13]) will show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and will aid in understanding of the benefit/risk evaluation. These patient-reported outcome (PRO) questionnaires are well-established instruments that have been previously included in lung cancer clinical trials.

The immunogenicity of durvalumab is being examined to assess its potential impact on safety and efficacy parameters. CCI [redacted]

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with durvalumab and the overall benefit/risk assessment.

1.3.1 Potential benefits

1.3.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab 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 ESMO 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 durvalumab Q2W was 39%, and the ORR was 15% (26% [12 out of 47 patients] with known PD-L1-positive NSCLC [i.e., ≥ 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 durvalumab Q2W had SD for ≥ 12 weeks (including 21% [10 out of 47 patients] with known PD-L1-positive NSCLC and 32% [24 out of 74 patients] with known PD-L1-negative NSCLC). Responses were ongoing in 88% of patients with NSCLC, with an objective response duration ranging from 0.1 to 32.4 weeks (Antonia et al 2014b).

PACIFIC study is a double-blind, placebo-controlled Phase III study of durvalumab after chemoradiation therapy in patients with Stage III, locally advanced, unresectable NSCLC. 713 patients with stage III unresectable NSCLC who have not progressed following definitive platinum-based concurrent chemoradiation were recruited. Durvalumab treatment demonstrated a statistically significant (HR: 0.51; 95% CI: 0.41, 0.63; p-value <0.0001) and clinically meaningful prolongation of PFS compared with placebo. Median PFS improvement of 11.6 months compared with placebo (17.2 vs 5.6 months). The dual primary endpoint OS was also statistically significant (HR: 0.68; 99.73% CI: 0.469, 0.997; p‑value 0.00251) and clinically meaningful prolonged in durvalumab arm compared with placebo. Median OS in durvalumab arm was not reached, compared with 28.7 months in placebo arm. The treatment effects were sustained over time: 12-month OS 83.1% (durvalumab) vs. 75.3% (placebo); 24-month OS 66.3% (durvalumab) vs. 55.6% (placebo) (Antonia et al 2018).

Data from ongoing studies with durvalumab 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 are PD-L1-positive.

1.3.2 Potential risks

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 diarrhoea, 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 Durvalumab

Risks with durvalumab 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(including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, 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 durvalumab, please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, AEs at an incidence of > 20% include events such as fatigue, cough, decreased appetite, dyspnea and nausea. Approximately 10% of patients discontinued the 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 durvalumab 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 see the Dosing Modification and the current version of Toxicity Management Guidelines in Dosing Modifications and Toxicity Management).

A detailed summary of durvalumab monotherapy 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 NSCLC who have not received prior chemotherapy or any systemic therapy for advanced NSCLC. The study design aims to minimize potential

risks such that 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., durvalumab 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 durvalumab in NSCLC and the strength of the scientific hypotheses under evaluation; the durvalumab treatment 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 improving quality of life (QoL) and potentially extending survival.

Therefore, the investigation of the potential therapeutic efficacy of durvalumab in patients with PD-L1-high expression tumors is acceptable, and the overall benefit/risk assessment supports the proposed study design.

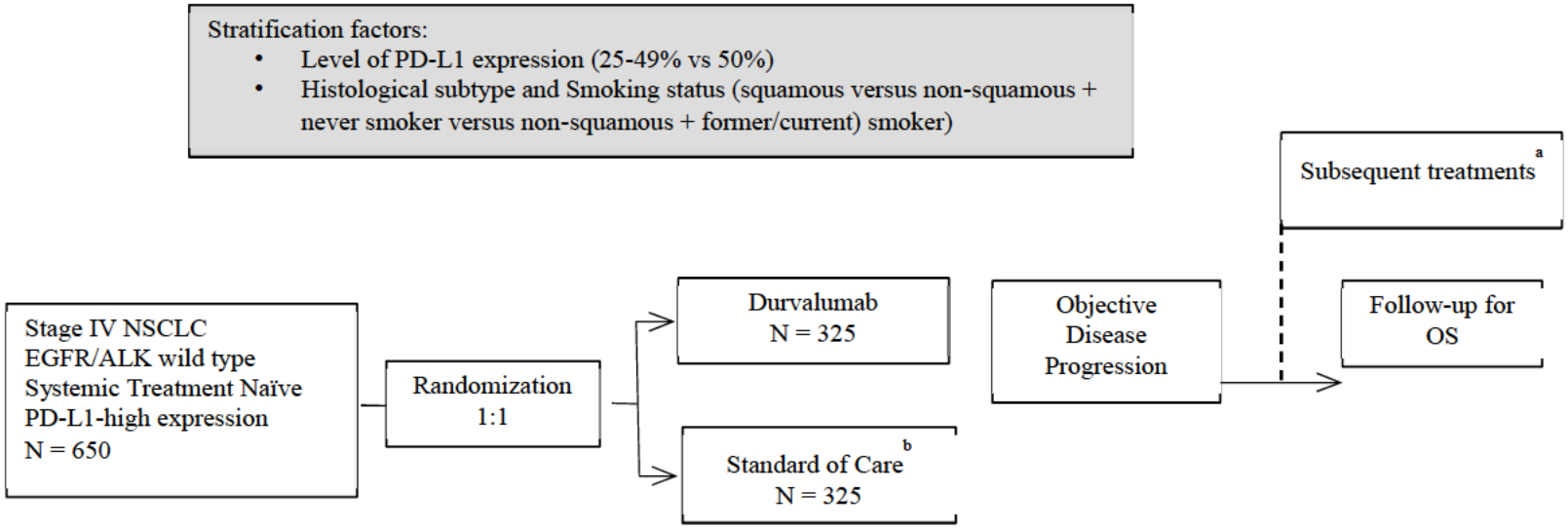
1.4 Study Design

This is a randomized, open-label, multi-center Phase III study to determine the efficacy and safety of and durvalumab versus platinum-based SoC chemotherapy in the first-line treatment of advanced NSCLC patients who are EGFR and ALK wild-type and have PD-L1-high expression. A schematic diagram of the overall study design is shown in Figure 1, and a detailed study flow chart is shown in Figure 2.The study will randomize approximately 650 patients from selected sites in China and other countries who will be randomized in a 1:1 ratio to 2 treatment arms (durvalumab or SoC therapy) in a stratified manner according to level of PD-L1 expression (25-49% versus ≥50%), histology and smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current smoker). This is to ensure the uniform distribution of main predictive factors of response, e.g. PD-L1 intensity and smoking status in each treatment group.

Patients will provide a tumor tissue sample at enrolment (newly acquired or archived sample <3 months old) to determine PD-L1 expression status (defined by the Ventana SP263 PD-L1 IHC assay in which ≥ 25% PD-L1membrane expression in tumoral tissue is considered as high expression.

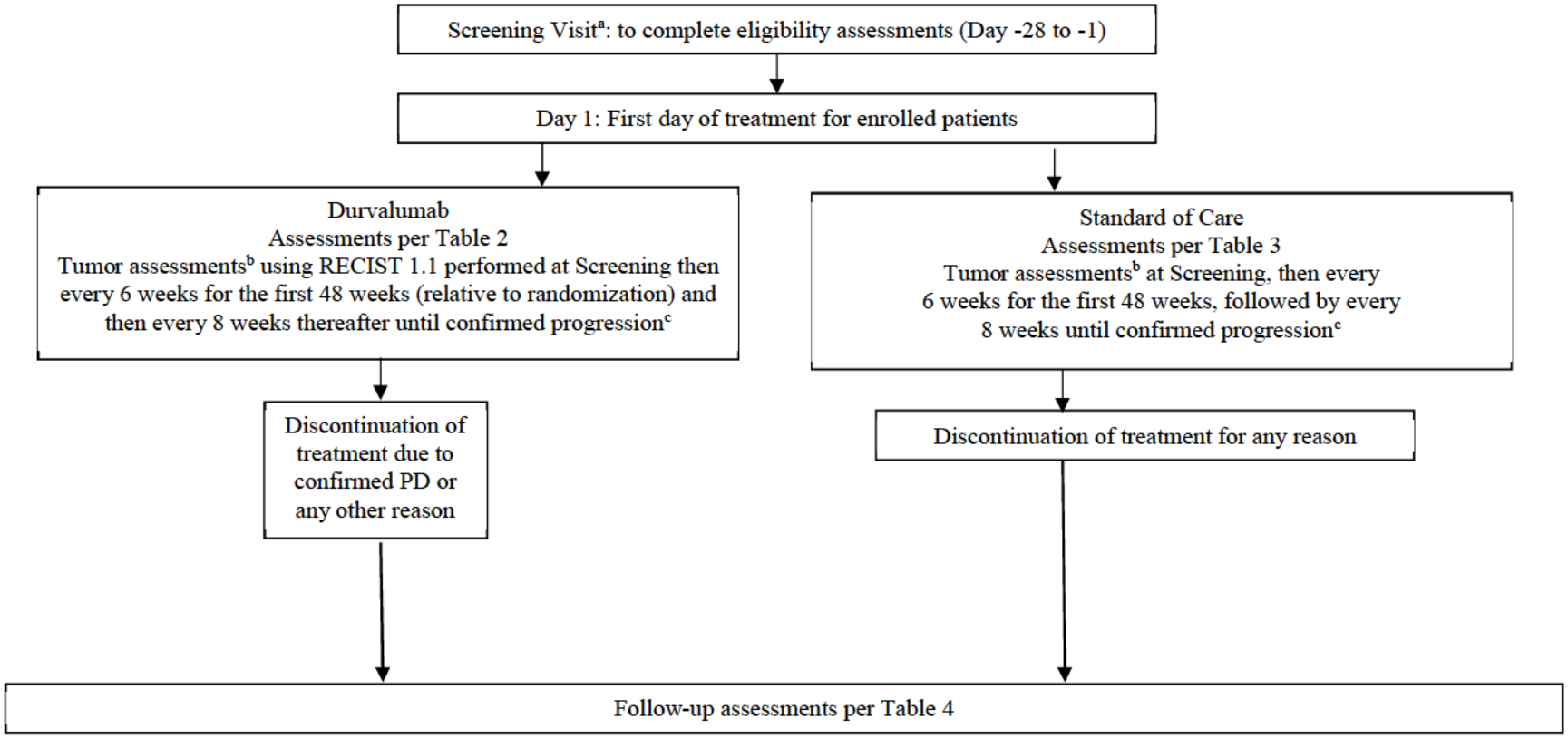
Doses and treatment regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 2, Table 3, and Table 4.

Figure 1 Overall study design



[a] Offer of subsequent therapy per Investigator discretion.
[b] Standard of Care 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



[a] 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 (PD-L1 status and, if unknown, EGFR and ALK status) prior to randomization.
[b] Tumor assessments were performed using RECIST 1.1
[c] A confirmatory scan is always required following the initial demonstration of PD and preferably at the next scheduled visit (in the absence of clinically significant deterioration).

1.4.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity. Where allowable by local health authorities, ethics committees, health care provider guidelines (e.g., hospital policies) or local government, these changes may include the following options:

- Obtaining [consent/reconsent] for the mitigation procedures (note, in the case of verbal [consent/reconsent], the informed consent form [ICF] should be signed at the participant's next contact with the study site).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix F.

2. STUDY OBJECTIVES

2.1 Primary objectives

Primary Objectives:	Outcome Measures:
To assess the efficacy of durvalumab compared to SoC in patients with PD-L1 TC ⩾ 25% (all randomized patients)	OS
To assess the efficacy of durvalumab compared to SoC in patients with PD-L1 TC ⩾ 25% and low risk of early mortality[a]	OS

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To assess the efficacy of durvalumab compared to SoC in terms of OS	OS in patients with • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality
To further assess the efficacy of durvalumab compared to SoC in terms of PFS, ORR, DoR, OS18, OS24, APF12, and PFS2	PFS, ORR, DoR, APF12 using Investigator assessments according to RECIST 1.1, PFS2 using local standard clinical practice, OS18 and OS24 respectively in patients with • PD-L1 TC ⩾ 25% • PD-L1 TC ⩾ 25% and low risk of early mortality • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality
To assess disease-related symptoms and HRQoL in patients treated with durvalumab compared to SoC using the EORTC QLQ-C30 v3 and the LC13 module	EORTC QLQ-C30, EORTC QLQ-LC13, and changes in Eastern Cooperative Oncology Group (ECOG) performance status in patients with • PD-L1 TC ⩾ 25% • PD-L1 TC ⩾ 25% and low risk of early mortality
To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab in patients with • PD-L1 TC ⩾ 25% • PD-L1 TC ⩾ 25% and low risk of early mortality

a. The population at low risk of early mortality consists of patients identified by a prognostic model developed by AstraZeneca as having low risk of early mortality.

2.3 Safety objective

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of durvalumab compared to SoC	AEs, physical examinations, laboratory findings, and vital signs

2.4 CCI [redacted]

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

[redacted]

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, 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 ≥18 years at the time of screening

2. Written informed consent obtained from the patient/legal representative prior to performing any protocol-related procedures, including PD-L1 testing and other screening evaluations.

3. Histologically or cytologically documented Stage IV NSCLC (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology; IASLC Staging Manual in Thoracic Oncology).

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 S7681 mutation) and ALK rearrangement.

5. Patient must have tumor cell PD-L1-high expression status, prior to randomization, defined as ≥25% PD-L1–membrane expression in tumoral tissue with the Ventana SP263 PD-L1 IHC assay determined by a reference laboratory. 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 screening. 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 CCI r analyses (if applicable) and is preferred in formalin-fixed paraffin embedded blocks.

6. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrolment

7. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.

8. Must have a life expectancy of at least 12 weeks.

3.2 Exclusion criteria

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

Cancer Related:

1. Prior chemotherapy or any other systemic therapy for advanced NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for locally advanced disease are eligible, provided that progression has occurred >6 months from last therapy.

2. Prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.

3. 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 study drug. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable.

4. 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. Asymptomatic brain metastases discovered during screening period must confirm stability in no less than 2 weeks by imaging (intravenous contrast-enhanced MRI (preferred) or IV contrast-enhanced CT). 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.

5. History of leptomeningeal carcinomatosis

6. Mixed small-cell lung cancer and NSCLC histology, sarcomatoid variant

Haematological, Biochemical, and Organ Function

7. Haemoglobin < 9.0 g/dL or haemoglobin ≥9.0 g/dL but with transfusion 4 weeks prior to the screening and randomization.

8. Absolute neutrophil count<1.5×10^9 /L.

9. Platelet count<100×10^9/L.

10. Serum bilirubin>1.5 × the ULN. This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.

11. ALT and AST >2.5 × ULN; for patients with hepatic metastases, ALT and AST >5 × ULN.

12. Calculated creatinine clearance <50 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine collection.

    Males:

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

    Females:

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

General:

13. 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, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhoea), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc. within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:

    – Patients with vitiligo or alopecia

    – Patients with hypothyroidism (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

14. History of active primary immunodeficiency.

15. Active infection, including tuberculosis (clinical evaluation), hepatitis B, hepatitis C, or human immunodeficiency virus (HIV, 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).

16. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. 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. 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.

19. History of allogenic organ transplantation.

20. History of another primary malignancy except for

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

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

- Adequately treated carcinoma in situ without evidence of disease (e.g., cervical cancer in situ)

21. Medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy.

22. Positive 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 ≥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).

23. Female patients who are pregnant or breast-feeding or male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 90 days after the last dose of durvalumab.

24. Known allergy or hypersensitivity to IP or any excipient or to other humanized mAbs.

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

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

27. 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, interstitial lung disease, or psychiatric illness/social situations that would limit compliance

with study requirement, substantially increase risk of incurring AEs from durvalumab, or compromise the ability of the patient to give written informed consent.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 3.4.

3.3 Patient enrolment and randomization

Investigators should keep a record (i.e., the patient screening log) of patients whose tumor tissue has been submitted for PD-L1 testing (and EGFR and ALK testing, if status unknown) and those patients who have entered screening.

Prior to treatment day (Day 1), the Investigator or suitably trained delegate will:

1. Obtain signed informed consent for **PD-L1 testing** and the main study using the main study ICF.

2. Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS in the following format PPD This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs). This "E#" is required prior to submission of the tumor sample for PD-L1 testing.

3. Obtain tumor sample and send for PD-L1 expression status evaluation. 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 in order to permit analysis prior to randomization.**

It is recommended that the sample to be sent only for the patient with known EGFR and ALK status. If EGFR and ALK status is unknown, the tumor sample (archive or fresh, primary or metastatic) can be used for (local or central) EGFR and ALK mutation testing in parallel with PD-L1 testing. If the local laboratory will perform the test, a well-validated, local regulatory-approved kit must be used. To complete the screening procedures during screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

4. Ensure the patient's PD-L1 status is available (and the EGFR and ALK status, if previously unknown). Whenever feasible, patients should be confirmed to have PD-L1-high expression and EGFR and ALK wild-type NSCLC before proceeding to complete other screening procedures.

5. Determine patient eligibility (see Sections 3.1 and 3.2)

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

6. 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.

   Note, for all patients with non-squamous tumor histology who are 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.

7. 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 either of the treatment groups.

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 treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrolment/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 study medication. 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 study treatment and for the specified times before and after:

1. Female patients of child-bearing potential

   – Female patients of childbearing potential who are not abstinent and intend to be 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 throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy).; Non-sterilised male partners of a female patient of childbearing potential must use a male condom plus spermicide (or male condom in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

   – Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

   – Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

   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.

- Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Highly effective methods of contraception, defined as 1 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 prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the SoC group.

3. All patients: Patients should not donate blood or blood components while participating in this study and for 90 days following the last dose of IP.

4. Restrictions relating to concomitant medications are described in Section 7.7.

The acceptable methods of contraception are described in Table 1. A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Not all methods of acceptable contraception are highly effective.

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

Barrier/Intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplan® • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP (durvalumab 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 (see ection 6.9.1) 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 study treatment (e.g., refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including another investigational agent

- Clinical progression, i.e. Investigator determination that the patient is no longer benefiting from treatment with IP, with or without radiological progression by RECIST 1.1.

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).

Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed Q6W ± 1w for the first 48 weeks (relative to the date of randomization), and then Q8W ± 1w thereafter until confirmed objective disease progression/death (whichever comes first) as defined in Table 2, Table 3 and Table 4.

If a patient is discontinued for unconfirmed progression then the patient should also continue to have RECIST scans performed Q6W ± 1w for the first 48 weeks (relative to the date of randomization), and then Q8W ± 1w thereafter until confirmed objective disease progression or until death (whichever comes first) as defined in Table 2, Table 3 and Table 4.

All patients will be followed for survival until the end of the study. If the study reaches statistical significance for OS at interim or final analyses, follow-up may continue in order to estimate the long-term benefit for durvalumab.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in Table 4 as an alternative.

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. The patient will return electronic PRO devices, if applicable.

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 attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, 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. (The SURVIVE module 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. (The SURVIVE module 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 study drug
- Are not considered to be consistent with continuation of the study

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 6.10).

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 durvalumab will remain open to enrolment and screening, if deemed appropriate by AstraZeneca.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and the treatment periods in this study are presented for the durvalumab group in Table 2 and for the SoC therapy group in Table 3. The procedures for the follow-up period are presented in Table 4. Patients who continue beyond C13 continue with all C13 assessments until termination of treatment (Table 2).

For all treatment arms

- PRO and 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 durvalumab monotherapy arm

- Patients may delay dosing under certain circumstances.

- Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related 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) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab (see current Investigator Brochures for durvalumab).

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 Durvalumab treatment period

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13[1] etc.	For details see Section
Week		**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44**	**48 etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309**	**337 etc.**	
Window (days)		**NA**	**+3[2]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Informed consent												
Informed consent	X[3]											4.1, 10.4
Study procedures												
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[4]		X	X	X	X	X	X	X	X	X	X	5.2.4

[1] Patients who continue on treatment will be assessed in the same manner
[2] Every effort should be made to minimize the time between randomization and starting treatment. (i.e. on the same day after randomization)
[3] 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 (PD-L1 status and, if unknown, EGFR and ALK status) prior to randomization.
[4] Body weight is recorded along with vital signs.

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13[1] etc.	For details see Section
Week		**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44**	**48 etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309**	**337 etc.**	
Window (days)		**NA**	**+3[2]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
ECG[5]		X	As clinically indicated									5.2.3
Concomitant medications	<----------										---------->	7.7
Demography, including baseline characteristics and tobacco use	X	X										4.1
Eligibility criteria	X	X										3.1, 3.2
Laboratory assessments[6]												
Clinical chemistry		X	X	X	X	X	X	X	X	X	X	Table 5
Hematology		X	X	X	X	X	X	X	X	X	X	Table 6

[5] Any clinically significant abnormalities detected require a confirmatory ECG.
[6] 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.

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13[1] etc.	For details see Section
Week		**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44**	**48 etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309**	**337 etc.**	
Window (days)		**NA**	**+3[2]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
APTT and INR		X	As clinically indicated									Table 6
TSH, free T_3, and free T_4[7]		X	X	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[8]		X	X	X	X	X	X	X	X	X	X	5.2.1
Monitoring												
WHO/ECOG performance status		X	X	X	X	X	X	X	X	X	X	5.3.3
AE/SAE assessment	<----------										---------->	6.3.1

[7] Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[8] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13[1] etc.	For details see Section
Week		**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44**	**48 etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309**	**337 etc.**	
Window (days)		**NA**	**+3[2]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Drug accountability			X	X	X	X	X	X	X	X	X	7.6
Pre-randomization medication[9]												
Folic acid		X	Discontinue as randomized to durvalumab									3.3
IM Vitamin B12		X	Discontinue as randomized to durvalumab									3.3
IP administration												
Durvalumab[10]			X	X	X	X	X	X	X	X	X	7.2.1
PRO assessments[11]												

[9] To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed if randomized to SoC group.
[10] Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion (within 3 days).
[11] In instances where the PRO assessments coincide with a clinic visit, the research nurse or study coordinator should verify that the questionnaire was completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13[1] etc.	For details see Section
Week		**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44**	**48 etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309**	**337 etc.**	
Window (days)		**NA**	**+3[2]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
EORTC QLQ-C30, CCI		X	Every 4 weeks for the first 8 weeks relative to the date of randomization, then every 8 weeks thereafter until second progression/death (whichever comes first)									5.3.1.1, 5.3.1.3
EORTC QLQ-LC13		X	Every 2 weeks for the first 8 weeks relative to the date of randomization, then every 4 weeks thereafter until second progression/death (whichever comes first)									5.3.1.2
Other laboratory assessments and assays												
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)			X			X			X			5.4.1
Tumor biopsy (newly acquired or archived <3 months old)	X[12]											5.5.1

[12] 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.

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8 to C12	C13[1] etc.	For details see Section
Week		-4 to -1	0	4	8	12	16	20	24	28, 32, 36, 40, 44	48 etc.	
Day	Prior to Day 1	-28 to -1	1	29	57	85	113	141	169	197, 225, 253, 281, 309	337 etc.	
Window (days)		NA	+3[2]	±3	±3	±3	±3	±3	±3	±3	±3	
EGFR and ALK test	X[13]											3.3
Tumor evaluation (CT or MRI) (RECIST 1.1)[14]		X	Every 6 weeks ± 1 week for the first 48 weeks relative to the date of randomization, and then every 8 weeks ± 1 week thereafter									5.1
Health economics measurements												
CCI [redacted]			To be completed at each hospitalization and unscheduled visit by site staff									8.5.9

Note: All assessments on treatment days are to be performed prior to infusion, 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; EORTC QLQ-C30 30-item core Eastern Cooperative Oncology Group Quality of Life Questionnaire; EORTC QLQ-LC13 13-item lung cancer EORTC QLQ; CCI [redacted]; HIV Human immunodeficiency virus; IM intramuscular; INR international normalized ratio; IP Investigational

[13] For patients with unknown status of ALK and/or EGFR NSCLC.

[14] 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 to and prior to the start of study treatment. 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. Treatment through confirmed radiologic PD for patients who may continue to benefit from the durvalumab at the discretion of investigator must be discussed on a case by case basis after consultation with the Sponsor

CCI [redacted]

product; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; PBMC Peripheral blood mononuclear cell; PD Progressive disease; SAE Serious adverse event; SNP Single nucleotide polymorphism; TSH Thyroid-stimulating hormone; T3 Triiodothyronine; T4 Thyroxine; WHO World Health Organization.

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

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc.	
Week		**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27, 30, 33, 36, 39, 42, 45, 48**	**51, 54, etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190, 211, 232, 253, 274, 295, 316, 337**	**358, 379, etc.**	
Window (days)		**NA**	**+3** [16]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Informed consent														
Informed consent	X[17]													4.1, 10.4
Study procedures														
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[18]		X	X	X	X	X	X	X	X	X	X	X	X	5.2.4

[16] Every effort should be made to minimize the time between randomization and starting treatment. (i.e., on the same day after randomization)
[17] 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
[18] Before every infusion or administration and as clinically indicated.

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

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc.	
Week		**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27, 30, 33, 36, 39, 42, 45, 48**	**51, 54, etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190, 211, 232, 253, 274, 295, 316, 337**	**358, 379, etc.**	
Window (days)		**NA**	**+3** [16]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
ECG[19]		X	As clinically indicated											5.2.3
Concomitant medications	<----------												---------->	7.7
Demography, including baseline characteristics and tobacco use	X	X												4.1
Eligibility criteria	X	X												3.1, 3.2
Laboratory assessments														
Clinical chemistry[20]		X	X	X	X	X	X	X	X	X	X	X	X	Table 5

[19] Any clinically significant abnormalities detected require a confirmatory ECG.
[20] To be collected every 3 weeks prior to the start of infusion and as clinically indicated. 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.

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

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc.	
Week		**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27, 30, 33, 36, 39, 42, 45, 48**	**51, 54, etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190, 211, 232, 253, 274, 295, 316, 337**	**358, 379, etc.**	
Window (days)		**NA**	**+3** [16]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Hematology[21]		X	X	X	X	X	X	X	X	X	X	X	X	Table 6
APTT and INR		X	As clinically indicated											Table 6
TSH, free T_3, and free T_4[22]		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[23]		X	As clinically indicated											5.2.1
Monitoring														

[21] To be collected every 3 weeks prior to the start of infusion and as clinically indicated. 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.
[22] Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[23] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

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

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc.	
Week		**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27, 30, 33, 36, 39, 42, 45, 48**	**51, 54, etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190, 211, 232, 253, 274, 295, 316, 337**	**358, 379, etc.**	
Window (days)		**NA**	**+3** [16]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
WHO/ECOG performance status		X	X	X	X	X	X	X	X	X	X	X	X	5.3.3
AE/SAE assessment	<----------												---------->	6.3.1
Pre-randomization medication[24]														
Folic acid		X	Continue in line with local practice											3.3
IM Vitamin B12		X	Continue in line with local practice											3.3
SoC administration														
Platinum-based chemotherapy			X	Cycle every 3 weeks										7.2.1

[24] To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed if randomized to SoC group.

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

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc.	
Week		**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27, 30, 33, 36, 39, 42, 45, 48**	**51, 54, etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190, 211, 232, 253, 274, 295, 316, 337**	**358, 379, etc.**	
Window (days)		**NA**	**+3** [16]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
PRO assessments[25]														
EORTC QLQ-C30, CCI [redacted]		X	Every 4 weeks relative for the first 8 weeks relative to the date of randomization, then every 8 weeks thereafter until second progression/death (whichever comes first)											5.3.1.1, 5.3.1.3
EORTC QLQ-LC13		X	Every 2 weeks for the first 8 weeks relative to the date of randomization, then every 4 weeks thereafter until second progression/death (whichever comes first)											5.3.1.2

[25] In instances where the PRO assessments coincide with a clinic visit, the research nurse or study coordinator should verify that the questionnaire was completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

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

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc.	
Week		**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27, 30, 33, 36, 39, 42, 45, 48**	**51, 54, etc.**	
Day	**Prior to Day 1**	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190, 211, 232, 253, 274, 295, 316, 337**	**358, 379, etc.**	
Window (days)		**NA**	**+3** [16]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Other laboratory assessments and assays														
Tumor biopsy (newly acquired or archived <3 months old)	X[26]													5.5.1
EGFR and ALK test	X[27]													3.3
Tumor evaluation (CT or MRI) (RECIST 1.1)[28]		X	Every 6 weeks ± 1 week for the first 48 weeks relative to the date of randomization, and then every 8 weeks ± 1 week thereafter											5.1

[26] 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

[27] For patients with unknown status of ALK and/or EGFR NSCLC.

[28] 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 to and prior to the start of study treatment. The radiological progression confirmatory scans should be performed no

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

	PD-L1 Testing	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10 to C17	C18, C19, etc.	
Week		-4 to -1	0	3	6	9	12	15	18	21	24	27, 30, 33, 36, 39, 42, 45, 48	51, 54, etc.	
Day	Prior to Day 1	-28 to -1	1	22	43	64	85	106	127	148	169	190, 211, 232, 253, 274, 295, 316, 337	358, 379, etc.	
Window (days)		NA	+3 [16]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	For details see Section
Health economics measurements														
CCI [redacted]			To be completed at each hospitalization and unscheduled visit by site staff											8.5.9

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; EORTC QLQ-C30 30-item core Eastern Cooperative Oncology Group Quality of Life Questionnaire; EORTC QLQ-LC13 13-item lung cancer EORTC QLQ; CCI [redacted]; HIV Human immunodeficiency virus; IM intramuscular; INR international normalized ratio; IP Investigational product; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; PBMC Peripheral blood mononuclear cell; PD Progressive disease; SAE Serious adverse event; TSH Thyroid-stimulating hormone; T3 Triiodothyronine; T4 Thyroxine; WHO World Health Organization.

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.

[redacted]

Table 4 Schedule of assessments for patients who have discontinued/completed treatment with Durvalumab or Standard of Care therapy

	Time since last dose of IP							
	Day (±3)	**Months (±1 week)**						**12 months and every 2 months (±2 weeks)**
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination (full)[1]	X							
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X							
Weight	X							
Pregnancy test[2]	X	As clinically indicated						
AE/SAE assessment[3]	X	X	X					
Concomitant medications	X	X	X					
WHO/ECOG performance status	At time points consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy[4]							

[1] Physical exams are described in Section 5.2.2.
[2] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.
[3] The AE/SAE follow-up for SoC is only 30 days
[4] 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 performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

Table 4 Schedule of assessments for patients who have discontinued/completed treatment with Durvalumab or Standard of Care therapy

	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
Subsequent anticancer therapy[5] and second progression assessment[6]	<----------							---------->
Survival status[7]		X	X	X	X	X	X	X
Hematology	X	X	X					
Clinical chemistry	X	X	X					
TSH, free T_3, and free T_4[8]	X							

[5] Details of any treatment for NSCLC (including surgery) post the last dose of study treatment must be recorded in the eCRF.
[6] 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. For patients who discontinue their assigned IP following confirmed progression, available readings of CT/MRI from local practice will be collected from the patients' medical charts while information on subsequent anticancer treatment and/or PFS2 is collected.
[7] 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 study treatment must be recorded in the eCRF.
[8] Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

Table 4 Schedule of assessments for patients who have discontinued/completed treatment with Durvalumab or Standard of Care therapy

	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
Immunogenicity assessment (ADA sampling) to identify ADA responses in patient circulation (durvalumab group only) [9]			X		X			
EORTC QLQ-C30, CCI [redacted]	Every 4 weeks relative for the first 8 weeks relative to the date of randomization, then every 8 weeks thereafter until second progression/death (whichever comes first)							
EORTC QLQ-LC13[11]	Every 2 weeks for the first 8 weeks relative to the date of randomization, then every 4 weeks thereafter until second progression/death (whichever comes first)							
CCI [redacted]	X							

[9] For patients in the durvalumab group only. Immunogenicity samples for durvalumab are collected 90 days (3 months) (± 7 days) after treatment with the applicable drug ends. In addition a final immunogenicity sample is taken 6 months (± 7 days) after treatment with the applicable drug ends.
[10] Patients will complete PROs using handheld devices at home.
[11] Patients will complete PROs using handheld devices at home.

Table 4 Schedule of assessments for patients who have discontinued/completed treatment with Durvalumab or Standard of Care therapy

	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
Tumor assessment (CT or MRI)[12]	Every 6 weeks ± 1 week for the first 48 weeks (relative to the date of randomization), and then every 8 weeks ± 1 week thereafter until confirmed objective disease progression/death (whichever comes first). Additional scans to be completed per standard practice post progression.[13]							

ADA Anti-drug antibody; AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; eCRF electronic case repot form; EORTC QLQ-C30 Eastern Cooperative Oncology Group Quality of Life Questionnaire; EORTC QLQ-LC13 EORTC QLQ Lung Cancer 13; CCI [redacted] IP Investigational product; MRI Magnetic resonance imaging; NSCLC Non-small-cell lung cancer; PD Progressive disease; PFS2 Time to second progression; RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; TSH Thyroid-stimulating hormone; T3 Triiodothyronine; T4 Thyroxine; WHO World Health Organization.

[12] Only for patients yet to progress, 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. The radiological progression confirmatory scans should preferably 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 scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

[13] If the patient continues to derive benefit from study treatment, then scans should continue to be collected following the original schedule and analysed by RECIST1.1, even after confirmed radiographic progression.

4.1 Enrolment/screening period

All screening and enrolment 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, and smoking history. 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 PD-L1 testing and other screening/baseline evaluations. 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).

Whenever feasible, patients must first be confirmed to have PD-L1-high expression and EGFR and ALK wild-type NSCLC before proceeding with the rest of screening procedures. Screening/baseline evaluations may be performed over more than 1 visit. Informed consent may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to screening completion and randomization. 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.

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, 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.

4.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule (see Table 4).

Whenever vital signs, 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.

For patients who require IP treatment to be held for toxicity and subsequently discontinue therapy without restarting IP, all follow-up assessments will be based on the date of the last dose of IP.

5. STUDY ASSESSMENTS

The Rave Web-Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the 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

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS, ORR, DoR and APF12 using Investigator assessment. 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, and OS will also be evaluated.

The assessment of tumor burden at baseline uses CT or MRI scans of the chest and abdomen (including liver and adrenal glands). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The baseline imaging assessment should be performed no more than 28 days before randomization and ideally as close as possible to the start of the assigned IP. Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks for the first 48 weeks (relative to the date of randomization; Table 2, Table 3, and Table 4) then Q8W thereafter, until confirmed objective disease progression per RECIST 1.1 (irrespective of the reason for stopping treatment or subsequent therapy). If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

For patients who discontinue IP (including SoC) due to toxicity in the absence of confirmed objective progression, objective tumor assessments per the scheduled assessments should be continued every 6 weeks for 48 weeks (relative to randomization) and then every 8 weeks until confirmed objective disease progression, every effort should be made to confirm a clinically significant deterioration by imaging.

A confirmatory scan is required for patients in both groups following prior demonstration of PD provided the subject is clinically stable. The confirmatory scan should occur no earlier than 4 weeks after the prior assessment of PD and preferably at the next scheduled imaging visit in the absence of clinically significant deterioration. Treatment with durvalumab or SoC may continue between the initial assessment of radiologic progression and confirmation of progression. Progression would be considered confirmed per RECIST 1.1 criteria available in Appendix D using Investigator assessments.

Radiologic progression would be considered confirmed if the following criteria are met:

- ≥ 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.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression. Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD, and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR or PR) and SD will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

Following confirmed progression, patients should continue to be followed up for survival every 1 to 2 months as outlined in the study plan (Table 4). Subsequent anticancer therapy information will be collected at time points indicated in Table 4.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans (Table 2 and Table 3 [screening and the treatment period] and Table 4 for follow-up of patients who have completed or discontinued IP treatment) and Appendix E.

5.1.1 Central reading of scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization (CRO) for quality control and storage. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. If a BICR is implemented, results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator.

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 analyses 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 and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 2, Table 3, and Table 4).

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).

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 coagulation), and Table 7 (urinalysis).

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum β-hCG) samples will be performed for pre-menopausal women of childbearing potential at Screening 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.

Other safety tests to be performed at Screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, HIV antibodies, thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), and free thyroxine (T_4).

Table 5 Clinical chemistry (serum or plasma)

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase[a]
Amylase[a]	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate[d]	Sodium
Calcium	Total bilirubin[b]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[c]	Uric acid

[a] In the event that amylase and lipase analyses cannot performed, 1 or the other will be performed in line with local practice.
[b] If total bilirubin is $\geqslant 2 \times$ ULN (and evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.
[c] At baseline and as clinically indicated.
[d] Bicarbonate (where available) is to be performed at baseline and if clinically indicated.

Table 6 Hematology and Coagulation

Hematology	
Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Haematocrit	Neutrophils
Haemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular haemoglobin	Total white cell count
Coagulation[a]	
Activated partial thromboplastin time	
international normalized ratio	

[a] Activated partial thromboplastin time and international normalized ratio are to be assessed at screening and as clinically indicated.

Table 7 Urinalysis

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

Bilirubin	Ketones
Blood	pH
Colour and appearance	Protein

Bilirubin	Ketones
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 ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN, refer to Appendix C for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. 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 (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IP (see Table 4).

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 study treatment 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 ECGs will be recorded at screening and as clinically indicated throughout the study (see Table 2, Table 3, and Table 4). 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, 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.

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. BP and pulse will be collected from patients in the durvalumab treatment group before, during, and after each infusion at the following times (based on a 60-minute infusion):

First infusion

On the first infusion day, patients in the durvalumab monotherapy 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.

Blood pressure (BP) and pulse will be collected from patients in the I-O arms 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 durvalumab.

Subsequent infusions

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 pre-dose and as clinically indicated before every infusion or administration.

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 Patient-reported outcomes

"PRO" is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered in this study: EORTC QLQ-C30 (core questionnaire), QLQ-LC13 (lung cancer module), and CCI (see Appendix E).

The PRO instruments will be completed by the patients using a handheld ePRO device. All assessments should be completed without assistance from anyone according to the assessment schedules (see Table 2, Table 3, and Table 4). It takes approximately 30 to 45 minutes for patients to complete the questionnaires; therefore, the burden to the patient is moderate.

5.3.1.1 EORTC QLQ-C30

The EORTC QLQ-C30 v3 questionnaire is included for the purpose of assessing HRQoL and is a well-established measure of HRQoL/health status, and commonly used as an endpoint in cancer clinical trials. It assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. Six single-item symptom measures are also included: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (see Appendix E). For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms (Aaronson et al 1993).

5.3.1.2 EORTC QLQ-LC13

For patients with NSCLC, a disease-specific 13-item self-administered questionnaire for lung cancer was developed (QLQ-LC13; Appendix E) to be used in conjunction with the EORTC QLQ-C30 (Bergman et al 1994). It comprises both multi-item and single-item measures of lung cancer-associated symptoms (i.e., coughing, hemoptysis, dyspnea, and pain) and side effects from conventional chemotherapy and radiotherapy (i.e., hair loss, neuropathy, sore mouth, and dysphagia). Similar to the EORTC QLQ-C30, all questions except 1 have a 4-point scale: "Not at all," "A little," "Quite a bit," and "Very much." One question (#43 "Did you take any medicine for pain?") has a response option of "Yes" or "No." The scoring approach for the QLQ-LC13 is similar to the EORTC QLQ-C30.

5.3.1.3 CCI

CCI

CCI

[redacted]

[redacted]

[redacted]

5.3.2 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using a handheld electronic device (ePRO).

Each center must allocate the responsibility for the administration of the PRO devices to a specific individual (e.g., a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be completed per the schedule of assessments (see Table 2, Table 3, and Table 4). Patients will be instructed to bring their handheld devices to every clinic visit. In instances where the PRO assessments coincide with a clinic visit, the research nurse or study coordinator should verify that the questionnaire was completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- The research nurse or appointed site staff must explain the value and relevance of participation to patients and inform them that these questions are being asked in order to find out from them directly how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patient has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor, and also provide guidance on whom to call if there are problems with the device.

- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items. The

patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.

- The research nurse or appointed site staff must monitor compliance; minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 85%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

5.3.3 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 changes from baseline or screening must be reported as an AE.

5.3.4 Pneumonitis (ILD) investigation

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 (see Section 6.9.1) 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 the eCRF. 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.

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumor markers: Particular tumor markers which are related to disease progression.
    (iii) Additional Clinical chemistry: CRP, LDH

5.4 ADA

5.4.1 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 durvalumab 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.

5.4.2 Storage and destruction of ADA samples

ADA samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the clinical study report (CSR).

ADA samples collected in China will be destroyed after the finalization of the bioanalytical report (or completion of 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.

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.

CCI
CCI Samples will be obtained according to the assessment schedules provided in Table 2 and Table 3.

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

All samples collected for biomarker analyses 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 durvalumab studies to evaluate biological responses across indications.

5.5.1 Collection of patient samples for PD-L1 testing

At screening, there is a mandatory provision of tissue to be used for determination of eligibility:

- 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 analyses (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. If a RECIST 1.1 target lesion is used for biopsy, the lesion must be $\geq$ 2 cm in the longest diameter and must be biopsied outside of the screening period.

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

CCI assay will be used to determine PD-L1 IHC status in this study for the purposes of eligibility assessment and for the analysis of the original diagnostic sample.

5.5.2 Exploratory biomarkers

CCI

[redacted]

5.5.3 CCI

CCI

[redacted]

CCI [redacted]

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 in the AstraZeneca Biobank Team during the entire life cycle.

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, and the study site informed.

- Ensure that the patient and AstraZeneca are informed about the sample disposal.

5.6 Pharmacogenetics

Not Applicable, Pharmacogenetic samples will not be collected in this study.

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 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 study treatment 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 durvalumab and 30 days after last dose of 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 fulfil 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., anaemia versus low haemoglobin 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. Further instruction on cases of increases in liver biochemistry and evaluation of Hy's law are shown in Appendix C.

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 study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. 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 Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. 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. It should also be documented in the Statement of Death page in the eCRF. 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 durvalumab treatment after final DCO and database closure, 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 durvalumab in order to manage AEs in accordance with the durvalumab toxicity management

guidelines (Dosing Modifications and Toxicity Management). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of Serious Adverse Events, will not otherwise be reported for the purposes of this study.

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.

6.2 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 fulfils 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
- 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 durvalumab 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 (report only the maximum CTCAE grade for a calendar day)
- 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
- 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)

- 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.

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 durvalumab.

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 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

6.6 Overdose

6.6.1 Durvalumab

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 durvalumab, 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 study drug 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.

6.6.2 Standard of Care

For patients randomized to the SoC group please refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE please record the AE/SAE diagnosis or symptoms in the relevant AE modules of the eCRF.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.7.1 Maternal exposure

Female patients must not become pregnant during the study and for up to 90 days after the last dose of durvalumab.

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 90 days after the last dose of durvalumab. 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 90 days after the last dose 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 (EC)/Internal Review Boards (IRB) prior to use.

6.8 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 patient or has the potential to cause harm to the patient.

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 patient.

Medication error includes situations where an error.

- Occurred.
- was identified and intercepted before the patient received the drug.
- did not occur, but circumstances were recognized 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 patient.
- 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 patient received the medication (excluding IVRS/IWRS errors).
- Wrong drug administered to patient (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.
- Subject accidentally missed drug dose(s) e.g. forgot to take medication.
- Accidental overdose (will be captured as an overdose).

- Subject 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.

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 i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.9 Management of investigational product-related toxicities

For guidance on the management of IP-related toxicities, please see Dosing Modifications and Toxicity Management.

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 of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- **It is important to note that these guidelines are prepared by the Sponsor to assist the Investigator in the exercise of his or her clinical judgment in treating these types of toxicities.**
- 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.

6.9.1 Specific toxicity management and dose modification information – Durvalumab

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 [MED4736] (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.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the Immune-mediated adverse event (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune-related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 3.9 of this protocol and the TMGs). Following the first dose of IP, subsequent administration of durvalumab 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 regimen by the reporting Investigator.

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

Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered prior to infusion at the discretion of the Investigator for primary prophylaxis against infusion-related reactions. In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of IP may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medications per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If the infusion-related reaction is Grade 3 or higher in severity, treatment with IP will be discontinued.

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

available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

6.9.2 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. 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 durvalumab 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 durvalumab 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 etiology. 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.

AESIs observed with durvalumab may include:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus)
- Rash/Dermatitis
- Nephritis
- Pancreatitis
- Myocarditis
- Myositis/polymyositis
- Neuropathy / Neuromuscular toxicity such as Guillain-Barré, and myasthenia gravis
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, 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 durvalumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Section 6.9.1). 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.

6.9.3 Standard of Care agents

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.

6.10 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 and received at least 2 cycles of treatment, 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 every 6 months thereafter until a decision to unblind the study is made. In addition, the IDMC will review the unblinded interim analysis summaries of efficacy data.

Full details of the IDMC procedures, processes, and interim analyses can be found in the statistical analysis plan and the IDMC Charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca will supply durvalumab (MEDI4736) while the SoC treatments (paclitaxel + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, pemetrexed + cisplatin,

pemetrexed + carboplatin, and pemetrexed maintenance) will be supplied locally unless central supply is required in participating country (Table 8).

Table 8 List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab (MEDI4736)	50 mg/mL, solution for infusion after dilution	MedImmune
Standards of Care		
Paclitaxel[a]	IV (as sourced locally)	Sourced locally
Carboplatin[a]	IV (as sourced locally)	Sourced locally
Gemcitabine[a]	IV (as sourced locally)	Sourced locally
Cisplatin[a]	IV (as sourced locally)	Sourced locally
Pemetrexed[a]	IV (as sourced locally)	Sourced locally

[a] Under certain circumstances when local sourcing is not feasible, a Standard of Care treatment may be supplied centrally by AstraZeneca.

7.1.1 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product should be kept in original packaging until use to prevent prolonged light exposure.

Preparation of Durvalumab (MEDI4736) doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

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

A dose of 20 mg/kg will be administered using an IV bag containing 0.9% weight/volume (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm filter. Add calculated volume (i.e. 20 mg/kg) of durvalumab (MEDI4736) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time 1 hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered or complete the infusion according to institutional policy to ensure the full dose is administered.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

Patient weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

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

Dose calculation

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

20 mg/kg × patient weight (kg) ÷ durvalumab (MEDI4736) concentration (nominal: 50 mg/mL).

Example: For a patient weighing 80 kg, dosed at 20 mg/kg, 32 mL [20 mg/kg × 80 kg divided by 50 mg/mL] of durvalumab (MEDI4736) is to be added to an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted durvalumab (MEDI4736) is administered as described above.

7.1.2 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, a 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 durvalumab or SoC.

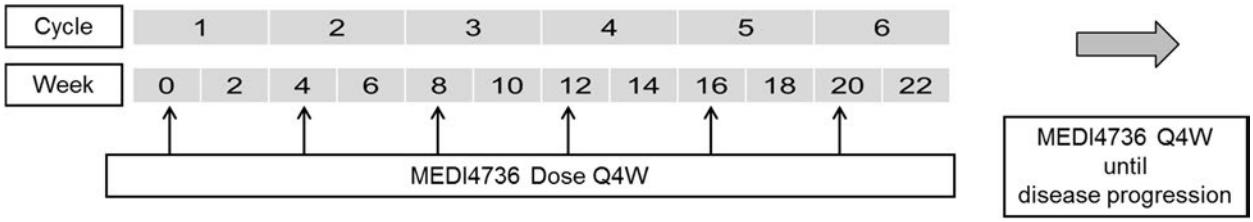
7.2.1 Treatment regimens

Durvalumab

Patients in the durvalumab treatment group will receive 20 mg/kg durvalumab (MEDI4736) via IV infusion Q4W unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (see Figure 3).

Standard infusion time is 1 hour. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Figure 3 Durvalumab (MEDI4736) dosing scheme



Standard of Care treatment

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

- Paclitaxel + carboplatin: Paclitaxel 175mg/m^2 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
- Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m^2 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^2 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^2 and cisplatin 75 mg/m^2 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^2 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 experienced recurrence or progression of disease within 6 months of prior multimodal therapy using that particular treatment.

A confirmatory scan is required for all patients in the SoC group, even if a subsequent treatment is started.

7.2.2 Duration of treatment

Duration of treatment

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

Progression during treatment

During the treatment period patients in both arms may continue receiving therapy in the setting of unconfirmed radiologic progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), at the Investigator's discretion, until progression is confirmed. A confirmatory scan is required following a RECIST 1.1 overall 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 all arms with PD by 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 immunotherapy arm 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 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 durvalumab.

For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing would not further benefit the patient.

Criteria for treatment in the setting of PD:

- Absence of clinical symptoms or signs that indicate clinically significant deterioration;
- Absence of any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not provide further benefit.

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 final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the scheduled DCO for final analysis and final database lock may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the scheduled DCO for final analysis, it is recommended that the patients continue the scheduled site visits.

Investigators should continue to monitor and document data for all study patients in the source notes after scheduled DCO for final analysis and final database lock. Dependent on the analysis results, a decision may be made to continue further data collection for a longer period with intent to analyze long-term OS and safety data to fulfill any other potential Health Authority requirements. Any additional long-term analysis may be further clarified through addendum to main statistical analysis plan, which will be developed before DCO for the long-term analysis. Data will be collected until any of following conditions are met:

- Until remaining patients in the study (including patients after discontinuation of study treatment) have discontinued the study *OR*
- Remaining patients have been transferred into a roll-over study *OR*
- If the sponsor decides to stop data collection, patients ongoing study treatment at this time and deriving clinical benefit from their assigned treatment will be allowed to continue treatment and only SAEs will be collected.

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 PEARL 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.

IP will be provided with either single panel labels or multi language booklet labels.

Label text prepared for durvalumab (MEDI4736) will show the product name as “MEDI4736” or “durvalumab (MEDI4736)” depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

7.4 Storage

The Investigator, or an approved representative (e.g., pharmacist), will ensure that Durvalumab is stored in original carton box, 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 study drugs (including IP) 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 study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs dispensed to and returned from the patient.

Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site, for all unused study drugs, and for appropriate destruction of study drugs. 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 days 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.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.9 for guidance on management of IP-related toxicities. For agents in the SoC arm, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Prohibited medication/class of drug:	**Usage:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment (including SoC)

Prohibited medication/class of drug:	Usage:
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment (including SoC).
Any concurrent chemotherapy, local therapy (except palliative radiotherapy, surgery, radiofrequency ablation for non-target lesions), biologic therapy, traditional Chinese Medicine, or hormonal therapy for the purpose of cancer treatment	Should not be given whilst the patient is on IP treatment (including SoC). (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable).
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and TNF-α blockers	Should not be given concomitantly (including SoC), or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Short-term premedication for patients receiving combination agent where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions. • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC) during the study.
EGFR TKIs	Should not be given concomitantly (including SoC). Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor.

Rescue/supportive medication/class of drug:	Usage:
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

Rescue/supportive medication/class of drug:	Usage:
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 above, which is 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.

As a result of imAEs that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressant rescue medication must be made available to this patient population.

7.7.2 Durvalumab drug drug interactions

There is no information to date on drug-drug interactions with durvalumab either pre-clinically or in patients. As durvalumab 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 durvalumab will induce or inhibit the major drug metabolising cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions. The mechanism of action of durvalumab 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 durvalumab (see Section 7.2.2).

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

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

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of the first patient randomization 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 durvalumab to SoC.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the SAP

8.2 Sample size estimate

The study will randomize approximately 650 eligible patients 1:1 to durvalumab or SoC.

The primary objectives of this study are to assess the efficacy of durvalumab compared with standard of care (SoC) in terms of overall survival (OS) in advanced NSCLC patients with EGFR and ALK wild-type and PD-L1-high expression (TC ≥ 25%) tumors, and in the PD-L1 TC ≥ 25% and low risk of early mortality population. To strongly control for type I error at a 5% level (2 sided), an alpha of 4% (2 sided) will be used for the OS comparison of durvalumab versus SoC in the PD-L1 TC ≥ 25% population, and an alpha of 1% (2 sided) will be used for the OS comparison of durvalumab versus SoC in the PD-L1 TC ≥ 25% and low risk of early mortality population. The study will be considered to have met its primary objective if any of the dual primary OS results are statistically significant.

There will be 2 data cut-offs in the study. The alpha will be split between the 2 OS analyses using the Lan and DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, with the boundaries for the treatment comparison derived based upon the exact number of OS events at the time of analysis to strongly control the overall type I error at a 5% level (2 sided).

One interim analysis to assess the superiority of the durvalumab group (compared to SoC group) in terms of OS will be performed when all of the following conditions have been met

- approximately 85% of the target 521 OS events (approximately 68% maturity) have been achieved across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% population
  And
- approximately 85% of the target 414 OS events (approximately 64% maturity) have been achieved across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% and low risk of early mortality population
  And
- a minimum 12 months follow-up from last patient randomized to the study.

The final (primary) analysis of OS will be performed when all of the following conditions have been met

- approximately 521 OS events (approximately 80% maturity) have occurred across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% population
  And

- approximately 414 OS events (approximately 76% maturity) have occurred across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% and low risk of early mortality population.

Durvalumab versus SoC (OS in the PD-L1 TC ≥ 25% population)

The sizing assumes a 6 months delay in separation of the OS curves between the two groups, hence the use of an average hazard ratio. If OS at 18 months was 46% with durvalumab and 36% with SoC (with a 12.9-month median OS [Chen, et al 2014, Ciuleanu et al 2009, Paz-Ares et al 2013, Scagliotti et al 2008] , i.e., Weibull distribution was assumed with shape parameter = 1.164459) and assuming the true average OS HR is 0.75, an estimated 521 death events (approximately 80% maturity) are expected to have occurred at 47 months from the time the first patient has been randomized with a 25-month recruitment period. With an estimated 521 deaths, the trial will have approximately 86% power to demonstrate statistical significance at the 2-sided alpha level of 3.334% (with overall alpha for OS 4%) for the comparison of durvalumab versus SoC, allowing for 1 interim analysis conducted at approximately 85% of the target events. The smallest treatment difference that could be statistically significant will be an average HR of 0.83.

Durvalumab versus SoC (OS in the PD-L1 TC ≥ 25% and low risk of early mortality population)

The sizing assumes a 3 months delay in separation of the OS curves between the two groups, hence the use of an average hazard ratio. If OS at 18 months was 52% with durvalumab and 39% with SoC (with a 13.8-month median OS, i.e., Weibull distribution was assumed with shape parameter = 1.164459) and assuming the true average OS HR is 0.69, an estimated 414 death events (approximately 76% maturity) are expected to have occurred at 46 months from the time the first patient has been randomized with a 25-month recruitment period. With an estimated 414 deaths, the trial will have approximately 87% power to demonstrate statistical significance at the 2-sided alpha level of 0.862% (with overall alpha for OS 1%) for the comparison of durvalumab versus SoC, allowing for 1 interim analysis conducted at approximately 85% of the target events. The smallest treatment difference that could be statistically significant will be an average HR of 0.77.

Non-uniform accrual of patients is assumed when estimating the analysis times. The total proportion of patients randomized at time t following the start of the study is assumed to be $(t/D)^{1.5}$, where D is the accrual duration.

8.3 Definitions of analysis sets

Definitions of the analysis sets are provided in this section and analysis sets for each outcome variable are provided in Table 9.

Table 9 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	

Outcome variable	Population
OS (primary)	Full analysis set (ITT population, i.e., PD-L1 TC ⩾ 25%)
OS (primary)	PD-L1 TC ⩾ 25% and low risk of early mortality analysis set
OS	PD-L1 TC ⩾ 50% analysis set
OS	PD-L1 TC ⩾ 50% and low risk of early mortality analysis set
PFS, ORR, DoR, OS18, OS24, APF12, PFS2, PROs, and symptom endpoints	Full analysis set (ITT population, i.e., PD-L1 TC ⩾ 25%)
PFS, ORR, DoR, OS18, OS24, APF12, PFS2, PROs, and symptom endpoints	PD-L1 TC ⩾ 25% and low risk of early mortality analysis set
PFS, ORR, DoR, OS18, OS24, APF12, PFS2	PD-L1 TC ⩾ 50% analysis set
PFS, ORR, DoR, OS18, OS24, APF12, PFS2	PD-L1 TC ⩾ 50% and low risk of early mortality analysis set
Demography	Full analysis set (ITT population, i.e., PD-L1 TC ⩾ 25%)
Demography	PD-L1 TC ⩾ 25% and low risk of early mortality analysis set
Safety Data	
Exposure	Safety analysis Set
	PD-L1 TC ⩾ 25% and low risk of early mortality safety analysis set
AEs	Safety analysis Set
	PD-L1 TC ⩾ 25% and low risk of early mortality safety analysis set
Laboratory measurements	Safety analysis Set
	PD-L1 TC ⩾ 25% and low risk of early mortality safety analysis set
Vital signs	Safety analysis Set
	PD-L1 TC ⩾ 25% and low risk of early mortality safety analysis set
ECGs	Safety analysis Set
	PD-L1 TC ⩾ 25% and low risk of early mortality safety analysis set

8.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients (i.e., patients with PD-L1 TC ≥ 25%). The full analysis set will be used for all efficacy analyses (including PROs). Treatment groups will be compared on the basis of randomized study treatment, regardless of

the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment group to which they were randomized.

8.3.2 PD-L1 TC ≥ 25% and low risk of early mortality analysis set

The PD-L1 TC ≥ 25% and low risk of early mortality population consists of patients identified by a prognostic model developed by AstraZeneca as having low risk of early mortality. The model is based on tumor type and six key routine laboratory parameters at baseline including NLR, neutrophils, albumin, lactate dehydrogenase, gamma glutamyltransferase and aspartate aminotransferase. All six parameters are required in the model. The model produces a score representing the probability of death occurring in ≤ 12 weeks for each patient. The model is then converted to a status that assigns patients to prognostic categories of high or low risk. Patients with a score above the cut-off are identified as high risk of EM, and patients at or below the cut-off are identified as low risk of EM. If any of the six parameters is missing, then the patient will be identified as unknown risk of EM.

8.3.3 PD-L1 TC ≥ 50% analysis set

The PD-L1 TC ≥ 50% analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 TC ≥ 50% as defined by the Ventana SP263 PD-L1 IHC assay (i.e., ≥ 50% of tumor cells with membrane positive for PD-L1).

8.3.4 PD-L1 TC ≥ 50% and low risk of early mortality analysis set

The PD-L1 TC ≥ 50% and low risk of early mortality population consists of patients with PD-L1 TC ≥ 50% and identified by a prognostic model developed by AstraZeneca as having low risk of early mortality.

8.3.5 Safety analysis set

The safety analysis set (SAS) will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized using the safety analysis set, 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.

8.3.6 PD-L1 TC ≥ 25% and low risk of early mortality safety analysis set

The PD-L1 TC ≥ 25% and low risk of early mortality safety analysis set will include patients identified by a prognostic model developed by AstraZeneca as having low risk of early mortality and who received at least 1 dose of study treatment.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

OS will be evaluated as a primary endpoint from all-cause mortality. The analysis of the secondary endpoints, PFS, ORR, DoR, and APF12, will be based on Investigator tumor

assessments according to RECIST 1.1. In addition, time to secondary progression (PFS2) will be defined by local clinical practice. 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 after 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.

8.4.1.1 Secondary endpoints

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 study treatment 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.

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

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 two consecutive missed visits. If the patient has no evaluable visits or does not have baseline data, they will be censored at day 1 unless they die within 2 visits of baseline.

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

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

- The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression.

- 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.

Objective response rate

ORR (per RECIST 1.1 using Investigator assessments) is defined as the percentage of patients with an unconfirmed 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.

Confirmed ORR which is defined as the percentage of patients with a confirmed response of CR or PR will be derived. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

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.

Proportion of patients alive at 18 months and 24 months from randomization

The proportion of patients alive at 18 months (OS18) and 24 months (OS24) will be defined as the Kaplan-Meier estimate of OS at 18 and 24 months.

Proportion of patients alive and progression free at 12 months

The APF12 will be defined as the Kaplan-Meier estimate of proportion of patients alive and progression free at 12 months based on PFS (per RECIST 1.1 as assessed using Investigator assessments) analysis.

Time from randomization to second progression (PFS2)

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. The site will be asked whether the patient has had a second progression event on a regular basis (every 6 weeks for the first 48 weeks relative to the date of randomisation and then every 8 weeks thereafter) following the first progression event used for the secondary variable PFS (the first progression) and the status recorded. Actual timing of assessments for a second progression event will, as mentioned, be according to local standard practice. 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 per RECIST 1.1 using Investigator assessments, described in Appendix D. It is the best response a patient has had during their time in the study, but prior to starting any subsequent cancer therapy, up until RECIST progression or the last evaluable assessment in the absence of RECIST 1.1 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 1.1 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 1.1 assessments prior to death.

For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs ≤91 days (i.e., 2*(6 weeks) + 1 week) 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 > 91 days (i.e., 2*(6 weeks) + 1 week after the date of randomization then BoR will be assigned to the NE category.

BoR based on confirmed response will also be derived.

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 and without worsening after the first dose 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 durvalumab, 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 durvalumab, 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 adverse events (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 study treatment.

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)] x 0.02)

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded.

The denominator in vital signs data should include only those patients with recorded data.

8.4.3 Calculation or derivation of patient-reported outcome variables

PRO questionnaires will be assessed using the EORTC QLQ-C30 with the QLQ-LC13 module (HRQoL and lung cancer specific symptoms), and CCI. All items/questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available.

8.4.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales/items from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorized as improvement, no change or deterioration as shown in Table 10.

Table 10 Mean change and visit response in health-related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-C30 Global quality of life score	⩾+10	Improvement
	⩽-10	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom scales/items	⩾+10	Deterioration
	⩽-10	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	⩾+10	Improvement
	⩽-10	Deterioration
	Otherwise	No change

For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Time to HRQoL/function/symptom deterioration

Time to deterioration will be analyzed for all QLQ-C30 scales/items. Dyspnea, fatigue and appetite loss from the QLQ-C30 will be key symptoms of interest. Time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration (a decrease in the function scales or the global health status/HRQoL from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to HRQoL/function deterioration. Patients with a single deterioration and no further assessments will be treated as deteriorated in the analysis.

Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the HRQoL/function change could be evaluated.

Patients whose HRQoL (as measured by EORTC QLQ-C30) has not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the HRQoL/function could be evaluated. Also, if HRQoL deteriorates after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where HRQoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at day 1.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥10 for EORTC QLQ-C30 symptom scales) in that symptom from baseline.

HRQoL/function improvement rate

The HRQoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score ≥10 for EORTC QLQ-C30 functional scales and global health status/HRQoL) in that scale from baseline.

8.4.3.2 Lung cancer module (EORTC QLQ-LC13)

The QLQ-LC13 is a lung cancer specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side-effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales/items from the QLQ-LC13 (Osoba et al 1998). For example, a clinically meaningful deterioration or worsening in chest pain (as assessed by the QLQ-LC13) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful improvement is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms from baseline will be categorized as an improvement, no change or deterioration as shown in Table 11.

Table 11 Visit response for health-related quality of life and disease-related symptoms

Score	Change from baseline	Visit response
QLQ-LC13 symptom scales/items	⩾+10	Deterioration
	⩽-10	Improvement
	Otherwise	No change

Time to symptom deterioration

For each of the following key symptom scales/items in the QLQ-LC13, time to deterioration will be analyzed:

- Dyspnea (multi-item scale based on 3 questions: were you short of breath when you rested; walked; climbed stairs)
- Cough: 1 item (how much did you cough?)
- Hemoptysis: 1 item (did you cough up blood?)
- Pain (3 individual items): a) Have you had pain in your chest; b) your arm or shoulder; c) other parts of your body?)

The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30.

Time to symptom deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom

deterioration. Patients with a single deterioration and no further assessments will be treated as deteriorated in the analysis.

Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by QLQ-LC13) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at day 1.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥10 for QLQ-LC13 symptom scales/items) in that symptom from baseline.

8.4.3.3 CCI

CCI

[redacted]

8.4.3.4 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab. 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 PDx, efficacy, and safety may be evaluated, if it provides further support for benefit risk assessment and if the data allow.

8.4.4 Calculation or derivation of biomarker variables

CCI [redacted]

8.5 Methods for statistical analyses

The formal statistical analysis will be performed to test the main hypotheses:

- H_0: No difference between durvalumab and SoC
- H_1: Difference between durvalumab and SoC

The 2 primary endpoints are OS in patients with PD-L1-high expression tumors (PD-L1 TC ≥25%) and OS in patients with PD-L1 TC ≥25% and low risk of early mortality.

One interim analysis to assess the superiority of the durvalumab group (compared to SoC group) in terms of OS will be performed when all of the following conditions have been met

- approximately 85% of the target 521 OS events (approximately 68% maturity) have been achieved across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% population
  And
- approximately 85% of the target 414 OS events (approximately 64% maturity) have been achieved across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% and low risk of early mortality population
  And
- a minimum 12 months follow-up from last patient randomized to the study.

The final (primary) analysis of OS will be performed when all of the following conditions have been met

- approximately 521 OS events (approximately 80% maturity) have occurred across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% population
  And
- approximately 414 OS events (approximately 76% maturity) have occurred across the durvalumab and SoC treatment groups in the PD-L1 TC ≥ 25% and low risk of early mortality population.

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 arm.

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 unless otherwise stated.

Results of all statistical analysis will be presented using appropriate 95% confidence intervals (CIs) and 2-sided p-values, unless otherwise stated.

The following table (Table 12) details which endpoints are subjected to statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint.

The efficacy and safety in China subgroup may be analysed to facilitate a benefit-risk assessment for regulatory submission in China. Details of this analysis will be specified in the Statistical Analysis Plan.

Table 12 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	Stratified log-rank test for: Primary analysis for the ITT population Primary analysis for the PD-L1 TC ⩾ 25% and low risk of early mortality population Secondary analysis for the PD-L1 TC ⩾ 50% population (stratified only for histology and smoking status) Secondary analysis for the PD-L1 TC ⩾ 50% and low risk of early mortality population (stratified only for histology and smoking status) Sensitivity analysis: max-combo test in: • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population
Progression-free survival	Stratified log-rank test for: Secondary analysis using Investigator RECIST 1.1 assessments • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population • PD-L1 TC⩾ 50% • PD-L1 TC⩾ 50% and low risk of early mortality population
Objective response rate	Logistic regression for: Secondary analysis using Investigator assessments (RECIST 1.1) • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality population

Endpoints analyzed	Notes
Duration of response	Kaplan-Meier estimates for Secondary analysis using Investigator assessments (RECIST 1.1) • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality population
Proportion of patients alive at 18 months (OS18) and 24 months (OS24)	Kaplan Meier estimates of survival rate at 18 months and 24 months in • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality population
Proportion of patients alive and progression free at 12 months	Kaplan Meier estimates of progression free survival at 12 months • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality population
Time from randomization to second progression	Stratified log-rank test • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population • PD-L1 TC ⩾ 50% • PD-L1 TC ⩾ 50% and low risk of early mortality population
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test in • ITT population • PD-L1 TC ⩾ 25% and low risk of early mortality population

Multiple testing strategy

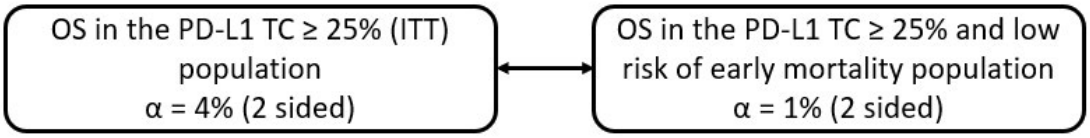
In order to strongly control the type I error at 5% (2-sided), a multiple testing procedure (MTP) with gatekeeping strategy will be employed across the 2 primary OS endpoints of OS in ITT population, OS in the PD-L1 TC ≥ 25% and low risk of early mortality population and selected secondary endpoints.

OS will be tested at 1 interim and a final time point. The OS tests for the same comparison (i.e., shown in 1 box in the MTP) will be considered as 1 test family. As long as one test in the family can be rejected, the family is rejected thus the assigned total alpha to the family can be recycled to the next MTP level. The testing procedure stops when the entire test mass is allocated to non-rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided) (Burman et al 2009).

The overall 5% type 1 error will be initially split between the 2 primary endpoints: an alpha level of 4% will be allocated to the analysis of OS in the ITT population and an alpha level of 1% will be allocated to the analysis of OS in the PD-L1 TC ≥ 25% and low risk of early mortality population. The first layer of MTP is shown in Figure 4. If either primary comparison is significant, the available alpha level will be recycled to the other primary comparison. If primary comparisons are both significant, the available alpha level may be recycled to other comparisons. The recycle scheme of these additional comparisons, if included in MTP, will be specified in SAP prior to DBL.

The alpha level allocated to OS will be controlled at the interim and final time points by using the Lan and Demets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends upon the proportion of information available. Separate Lan DeMets spending functions will be used for 2 primary endpoints and secondary endpoints.

Figure 4 First layer of the multiple testing procedure for controlling type I error rate



Note: alpha recycling between two dual primary OS comparisons.

8.5.1 Analysis of two primary endpoints – overall survival

Primary analysis of OS in the ITT population will be performed using a stratified log-rank test, adjusting for level of PD-L1 expression 25-49% versus ≥50% and histology and smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current smoker). The effect of durvalumab versus SoC will be estimated by the HR from stratified Cox proportional hazards model together with its corresponding CI and p-value (Cox 1972). Primary analysis of OS in the PD- L1 TC ≥ 25% and low risk of early mortality population will be conducted in the same manner.

A secondary analysis of OS will be performed using a stratified log-rank test, adjusting for only histology and smoking status using the PD-L1 TC ≥ 50% analysis set, and the PD- L1 TC ≥ 50% and low risk of early mortality analysis set. The corresponding HR will be estimated using a stratified Cox model.

The max-combo test will be conducted as a sensitivity analysis on the OS data in both the ITT and the PD- L1 TC ≥ 25% and low risk of early mortality population, to test for treatment differences in the case of nonproportional hazards. The analysis will be based on adaptive

procedure involving selection of best test statistics with log rank test ($G_{0,0}$) and the Fleming-Harrington (FH) test ($G_{0,1}$, $G_{1,0}$ and $G_{1,1}$) with alpha correction (Lin et al 2019).

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

The boundaries (i.e. adjusted alpha levels) for the treatment comparison at the interim and final analyses for OS will be derived based upon the exact number of OS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function (see Section 8.2).

Subgroup analyses will be conducted comparing OS between durvalumab versus SoC in the following subgroups of the FAS (but not limited to):

- Sex (male versus female)
- Age at randomization (<65 versus ≥65 years of age)
- Level of PD-L1 expression (25-49% vs ≥50%)
- Histology and Smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current)
- Region (China versus other)
- Race (Asian versus Non-Asian)
- Baseline liver metastases (Yes versus No)
- Baseline ECOG (0 versus >=1)
- Baseline risk status of early mortality identified by a prognostic model developed by AstraZeneca (Low risk, High risk, Unknown)

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 analyses 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 analyses will be made since all these analyses will be considered supportive of the primary analysis of OS.

Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. Before embarking on more detailed modeling, an initial model will be constructed, containing treatment and the stratification factors alone, to ensure that any output from the Cox modeling is likely 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 and 95% 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 analyses 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.

The efficacy and safety in China subgroup will be analyzed to facilitate a benefit-risk assessment for regulatory submission in China. Details of the Subgroup analysis will be specified in Statistical Analysis Plan.

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8.5.2 Progression-free survival

The main PFS analyses will be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments. The secondary analysis will be performed using a stratified log-rank test adjusting for level of PD-L1 expression 25-49% versus ≥50% and histology and smoking status (squamous versus non-squamous + never smoker versus non-squamous + former/current smoker). The effect of durvalumab versus SoC treatment will be estimated by the HR from stratified Cox proportional hazards model together with its corresponding 95% CI and p-value (Cox 1972). This analysis will be performed in the analysis sets as mentioned in Table 12.

Kaplan-Meier plots of PFS will be presented by treatment group, where appropriate. 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 analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment will be 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.

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using Investigator assessments) between durvalumab versus SoC using the same methodology as described in Section 8.5.1 for primary endpoint of OS.

8.5.3 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using the Investigator tumor data. ORR will be compared between durvalumab versus SoC using logistic regression models adjusting for the same factor as the primary endpoint (level of PD-L1 expression, histology and smoking status). 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 as mentioned in Table 12.

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 (i.e., the FAS). For each treatment group, best objective response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analysis is planned for BoR.

Analysis of confirmed ORR/BoR will also be conducted in the similar manner.

8.5.4 Duration of response

Descriptive data will be provided for the duration of response including the associated Kaplan-Meier curves (without any formal comparison or p-value attached). This analysis will be performed in the analysis sets as mentioned in Table 12.

DoR will also be assessed for the subgroup of patients who had a confirmed response.

8.5.5 Proportion of patients alive at 18 months and 24 months

The OS18 and OS24 will be summarized (using the Kaplan-Meier curve) and presented by treatment arm.

This analysis will be performed in the analysis sets as mentioned in Table 12.

8.5.6 Proportion of patients alive and progression free at 12 months

The APF12 will be summarized (using the Kaplan-Meier curve) and presented by treatment arm.

This analysis will be performed in the analysis sets as mentioned in Table 12.

8.5.7 Time from randomization to second progression

PFS2 is 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. It will be assessed using local practice guideline. PFS2 will be analyzed using a stratified log-rank tests, using the same methodology as described for the PFS endpoint. The effect of durvalumab 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 arm and the time between progression and starting subsequent therapy will be assessed. No multiplicity adjustment will be applied as these are viewed as supportive endpoints.

A summary table of first subsequent therapies by treatment arm will be provided, as well as response to first subsequent therapy by treatment arm.

This analysis will be performed in the analysis sets as mentioned in Table 12.

8.5.8 Patient reported outcomes

Any formal comparison for PRO in the MTP will be included in the SAP. The analysis of PRO data will be performed in the analysis sets as mentioned in Table 12.

8.5.8.1 EORTC QLQ-C30

Time to deterioration will be analyzed using a stratified log-rank test, using the same methodology as described for the primary OS endpoint.

The effect of durvalumab versus SoC will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. 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.

A summary of the symptom improvement rate for each of the 3 symptom scales and the 5 individual symptom items will be produced. Similarly, a summary of QoL/function

improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced.

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score and each functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal item (in terms of the proportion of patients in the categories of improvement, no change, and deterioration as defined in Section 8.4.3) will also be produced for each treatment arm.

8.5.8.2 EORTC QLQ-LC13

Time to deterioration will be analyzed using a stratified log-rank test, using the same methodology as described for the primary OS endpoint.

The effect of durvalumab versus SoC will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. 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.

A summary of the symptom improvement rate for each of the 6 individual symptom items will be produced.

Summaries of original and change from baseline values of each symptom (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, other pain) and each treatment-related side effect (sore mouth, dysphagia, peripheral neuropathy and alopecia) will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal symptom item (in terms of the proportion of patients in the categories of improvement, no change, and deterioration as defined in Section 8.4.3) will also be produced for each treatment arm.

8.5.8.3 CCI

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8.5.9 CCI

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8.5.10 Safety data

Safety and tolerability data will be presented by treatment arm using the analysis sets in Table 12.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to durvalumab and SoC will be summarized. Time on study, durvalumab, 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.

8.5.11 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-durvalumab antibody. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab antibody.

The effect of immunogenicity on efficacy and safety may be evaluated if it provides further support for benefit risk assessment and if data allow.

8.5.12 CCI

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8.5.13 Interim analysis

Interim safety monitoring will be conducted by an IDMC. Details of the plan and communication process will be provided in an IDMC Charter. One OS interim analysis is planned for durvalumab versus SoC in the ITT population as well as in the PD- L1 TC $\geq$ 25% and low risk of early mortality population. The interim analysis of OS will be conducted when approximately 444 OS events have occurred (approximately 85% of the target 521 OS events, i.e., approximately 68% maturity) in the ITT population; approximately 350 OS events have occurred (approximately 85% of the target 414 OS events, i.e., approximately 64% maturity) in the PD- L1 TC $\geq$ 25% and low risk of early mortality population and a minimum 12 months follow-up from last patient randomized to the study (whichever occurs later). This analysis will be performed by an IDMC.

The Lan and DeMets spending function that approximates an O'Brien Fleming approach will be used to account for multiplicity introduced by including the 1 interim analysis for superiority (Lan and DeMets 1983).

The criterion for superiority is a statistically significant improvement in OS at the interim analysis. If exactly 85% of the OS events required at the time of the final OS analysis are available at the time of the interim analysis, the 2-sided significance level to be applied for the OS in the ITT population at the interim and final analysis would be 2.325% and 3.334%, respectively; and the 2-sided significance level to be applied for the OS in the PD- L1 TC ≥ 25% and low risk of early mortality population at the interim and final analysis would be 0.466% and 0.862% respectively.

If the interim analyses indicate superiority, then subsequent analyses of the further secondary endpoints will be performed.

If the interim results do not meet the criterion of stopping for superiority, then follow-up will continue. OS will be retested at the final 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, WBDC, and any electronic PRO 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 study drug accountability checks are being performed

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

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, 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.

9.2.3 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 Q1 2017 and end by Q1 2021.

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 durvalumab.

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 Harmonisation (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

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.

AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.

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 enrolment 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 enrolment 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 IIP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each 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.

10.5 Changes to the protocol and informed consent form

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 (revised clinical study protocol).

The amendment 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 revised protocols.

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.

If required by local regulations, any administrative change will be communicated to or approved by each EC/IRB.

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.

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Appendix A Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

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

Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

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

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

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

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

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

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

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

Labelling and shipment of biohazard samples

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

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are 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 Section 6.9 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) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

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

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

Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

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

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

- Determine whether the patient meets PHL criteria (see Definitions within this Dosing Modifications and Toxicity Management or definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

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

- Notify the AstraZeneca representative.
- Determine whether the patient meets PHL criteria (see Definitions within this Dosing Modifications and Toxicity Management or definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF.

Follow-up

Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team

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

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

Review and Assessment of Potential Hy's Law Cases

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

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

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

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

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

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

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

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

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

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

Actions Required for Repeat Episodes of Potential Hy's Law

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

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

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

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

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

If Yes:

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

- If there is no significant change no action is required.
- If there is a significant change follow the process described in 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

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 the D419AC00002 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

Definition of measurable, non-measurable, target and non-target lesions

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

Tumor lesions selected for screening biopsy should not be selected as target lesions, unless imaging occured at least 2 weeks after biopsy, allowing time for healing.

Measurable:

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

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm to <15 mm short axis at baseline[1]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and, abdominal masses/abdominal

[1] The short axis is defined at the longest axis perpendicular to the long axis of the tumor. Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

organomegaly identified by physical examination that is not measurable by CT or MRI.

- Tumor lesions selected for screening biopsy
- Previously irradiated lesions[2]
- Skin lesions assessed by clinical examination
- Brain metastasis

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these 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:

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

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 13, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

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

Table 13 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 intravenous contrast, are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

It is recommended that intravenous contrast-enhanced CT examinations of the chest and abdomen (including liver and adrenal glands) are 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 intravenous CT contrast, a non-contrast CT examination of the chest and an MRI with intravenous contrast of the abdomen and pelvis is appropriate. In patients with severely compromised renal function a non-contrast CT examination of the chest, abdomen and pelvis is appropriate. For brain lesion assessment, MRI with intravenous 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 timepoints 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
18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will

be recorded where there is positive 18-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT 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 tumor 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 intravenous contrast) to a dedicated diagnostic CT scan, then the CT portion 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 to the start of investigational product. Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks for the first 48 weeks (relative to the date of randomization; see Section 3.1 of the Clinical Study Protocol), then every 8 weeks thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment/or subsequent therapy). If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

For patients who discontinue study drug due to toxicity in the absence of confirmed objective progression, objective tumor assessments should be continued every 6 weeks for 48 weeks (relative to the date of randomization) then every 8 weeks until confirmed objective disease progression.

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

Radiologic progression (PD by RECIST 1.1) requires confirmation; the confirmatory scan should occur no earlier than 4 weeks after the prior assessment of PD in the absence of clinically significant deterioration.

If progression is not confirmed then the patient should continue on study treatment 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 their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

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

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 two or more parts, then record the sum of the diameters of those parts.

- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g., radiotherapy, embolization, surgery, 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 14).

Table 14 Evaluation of target lesions

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

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

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 15).

Table 15 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. 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 one 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 one or more new lesions is assessed as progression.

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

The finding of a new lesion should be unequivocal: 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 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 16.

Table 16 Overall visit response

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

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

Radiologic progression (PD by RECIST 1.1) requires confirmation with a subsequent scan, and the confirmatory scan should occur no earlier than 4 weeks after the prior assessment of progression of disease (PD) in the absence of clinical deterioration.

Radiologic progression would be considered confirmed if the following criteria are met:

- ≥ 20% increase in sum diameters of target lesions compared to the nadir at 2 consecutive visits (with an absolute increase of at least 5 mm)
- *And/or* significant progression (worsening) of NTLs at the follow-up scan time-point compared with the immediate prior time-point
- *and/or* significant progression (worsening) of pre-existing new lesions[4] at the follow-up scan timepoint compared with the immediate prior timepoint (Note: Pre-existing

[4] A new lesion is considered new only at the visit it was first identified—in all subsequent visits, it will be considered a pre-existing 'new' lesion and will still need to be recorded if present.

new lesions from earlier time-points are evaluated as NTLs at the confirmatory scan time-point)

- And/or additional new unequivocal lesions at the confirmatory scan time-point.

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

If radiologic progression is not confirmed, then the patient should continue on study treatment and continue with regularly scheduled imaging assessments.

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

Central Review
Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization (CRO) for quality control and storage. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. If a BICR is implemented, results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator.

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(2):228-47.

Appendix E Patient Reported Outcomes

EORTC QLQ-C30, EORTC QLQ-LC13, AND CCI

EORTC QLQ-C30 (Version 3)

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

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

During the past week:

6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4

15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

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

During the past week :		**Not at all**	**A little**	**Quite a bit**	**Very much**
1.	How much did you cough?	1	2	3	4
2.	Did you cough up blood?	1	2	3	4
3.	Were you short of breath when you rested?	1	2	3	4
4.	Were you short of breath when you walked?	1	2	3	4
5.	Were you short of breath when you climbed stairs?	1	2	3	4
6.	Have you had a sore mouth or tongue?	1	2	3	4
7.	Have you had trouble swallowing?	1	2	3	4
8.	Have you had tingling hands or feet?	1	2	3	4
9.	Have you had hair loss?	1	2	3	4
10.	Have you had pain in your chest?	1	2	3	4
11.	Have you had pain in your arm or shoulder?	1	2	3	4
12.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
13.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

CCI

CCI


CCI

Appendix F Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

F 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, e.g., remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections F 2 to F 3. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

F 2 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medicationadd other information including efficacy data where relevant to be collected according to study requirements to be reported and documented.

F 3 Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by the qualified HCP from the study site in the source documents, or by the participant themselves.

F 4 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section F6). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

F 5 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section F7 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab. The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

F 6 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with

logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

F 7 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

F7.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

F7.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

F7.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (e.g., confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

F7.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

F 8 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

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