AstraZeneca

Statistical Analysis Plan

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A Phase IIIb, Single-arm, Multi-center, International Study of Durvalumab in Combination with Platinum and Etoposide for the First Line Treatment of Patients with Extensive-stage Small Cell Lung Cancer (LUMINANCE)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BoR	Best objective response
BP	Blood Pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Complete Response
CrCl	Creatinine Clearance
CS	Clinically significant
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CCI	CCI
DBL	Database lock
DBP	Diastolic blood pressure
DCO	Data cut-off
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
CCI	CCI
CCI	CCI

Abbreviation or special term	Explanation
ES-SCLC	Extensive-stage Small Cell Lung Cancer
CCI	CCI
ICH	International conference of harmonisation
ICH 1995	ICH guidelines version dated 1995
imAE	Immune-mediated adverse event
IMP	Investigational medicinal product
IO	Immuno-Oncology
IPD	Important protocol deviations
IV	Intravenous
kg	Kilogram
LLQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of action
MRI	Magnetic resonance imaging
msec	Milliseconds
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NTL	Non-target lesion
ORR	Overall response rate
OS	Overall survival
OS12	Proportion of patients alive at 12 months
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PFS12	Proportion of progression-free and alive patients at 12 months
PR	Partial response
CCI	CCI
PS	Performance status

Abbreviation or special term	Explanation
PT	Preferred term
q3w	Every three weeks
q4w	Every four weeks
CCI	CCI
CCI	CCI
CCI	CCI
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	Relative dose intensity
RECIST1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
CCI	CCI
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBP	Systolic blood pressure
SD	Stable disease
SI	International system (of units)
SOC	System organ class
T3	Tri-iodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TL	Target lesion
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
12 July 2021	Initial version 1.0
22 September 2021	Version 1.1 includes the following changes from V1.0: • Additions or revisions: • a change in the PFS unit from days to months (Section 3.2.2) • addition of definition of missed visits for PFS (Section 3.2.2) • a change in the OS unit from days to months (Section 3.2.3) • a change in the DoR unit from days to months (Section 3.2.6) • addition of output presentation by ECOG group (Section 4.1.1) • CCI [redacted] • changes to the summaries and analysis set of patient disposition (Section 4.2.1) • changes to the categories for presentation for demography and baseline characteristics (Section 4.2.3) • changes to the summaries of adverse events leading to discontinuation or interruption (Section 4.5.1) • addition of COVID-19 related adverse events analysis (Section 4.5.1) • changes to the presentation of adverse event by SOC and PT and maximum CTCAE grade. Causality removed (Section 4.5.1) • addition of text for most common adverse event (Section 4.5.1) • changes to the presentation of adverse event of special interest by PT, seriousness and maximum CTCAE grade. Causality removed (Section 4.5.1.1) • addition of Absolute leukocytes count parameter to Haematology (Section 4.5.4) • addition of new categories for ALT, AST and ALT or AST (Section 4.5.4.1) • addition of new text for Shift table for TSH test (Section 4.5.4.2) • Removed section 4.5.4.3 Assessment of Renal Function Test Abnormalities • Changes to summaries for overdose and medical error (Section 4.5.6) • Schedule of assessment removed from Appendix
13th May 2022	• Section 4.5.1.1- AEPI category added • Section 4.5.1- The AE for etoposide+platinum are now separated

Date	Brief description of change
02 November 2022	into etoposide and platinum Section 5 – Early safety evaluation added in interim analysis section. • Section 4.5.1-The AEs for etoposide+platinum is presented together as per suggestion from Sponsor. • Section 4.5.1-The cut-off for most common AEs with CTCAE Grade 3 or higher has been changed from =>2.5 to >2.5 • Section 4.5.1-Summary of most common AEs with CTCAE Grade 3 or higher is added for patients who had less than <=4 cycles of EP and >4 cycles of EP • 3.2.5 (Best objective response definition) added
07 June 2023	Section 14.1.1 For RECIST and ECOG, baseline assessment
12th June 2023	The timing of primary analysis is mentioned in section 5 Added 'any study treatment' for safely population ins section 2.1 Added 'as per RECIST 1.1' in progression free survival definition in section 3.2.2 Reference to SURVIVE AND DEAETH module removed

1. STUDY DETAILS

This is an open-label, single-arm, multi-center, international, Phase IIIb study to determine the safety and tolerability profile of durvalumab with platinum (cisplatin or carboplatin) plus etoposide (EP) as first-line treatment in patients with extensive-stage small-cell lung cancer. The study will be conducted in North America and Europe.

1.1.1 Primary Objective

Primary Objective	Endpoint / Variable
To assess the safety and tolerability profile of durvalumab + EP treatment	Incidence of Grade ≥ 3 AE Incidence of imAEs

Note: Toxicities will be classified as per NCI CTCAE grading system version 5.0.

Note: An 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.

imAE: immune-mediated adverse event; CTCAE: Common Terminology Criteria for Adverse Event; EP: platinum (cisplatin or carboplatin) plus etoposide; NCI: National Cancer Institute.

1.1.2 Secondary Objectives

Secondary Efficacy Objectives	Endpoints / Variables
To assess the efficacy of durvalumab + EP treatment	PFS, ORR, DoR, DoR12, and PFS12 using site Investigator assessments according to RECIST 1.1 OS and OS12
Secondary Safety Objectives	**Endpoints / Variables**
To further assess the safety and tolerability profile of durvalumab + EP, including all AEs	Incidence of AEs, SAEs, AESIs, AE resulting in treatment discontinuation, and laboratory findings including clinical chemistry, hematology and urinalysis

Note: Toxicities will be classified as per NCI CTCAE grading system version 5.0.

Note: Analysis of ORR and DoR will be based upon Investigator assessment according to RECIST 1.1. Prior irradiated lesions may be considered measurable and selected as target lesions (TLs) provided they fulfil the other criteria for measurability.

Note: An AESI is an AE of scientific and medical interest specific to understanding of the IMP. 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.

AE: adverse event; AESI: adverse event of special interest; DoR: duration of response; DOR12: proportion of patients remaining in response 12 months from the time of first documented objective response; EP: platinum (cisplatin or carboplatin) plus etoposide; ORR: objective response rate; OS: overall survival; OS12: proportion of patients alive at 12 months from first date of treatment; PFS: progression-free survival; PFS12: proportion of patients alive and progression-free at 12 months from first date of treatment; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SAE: serious adverse event.

1.1.3 CCI

CCI

CCI

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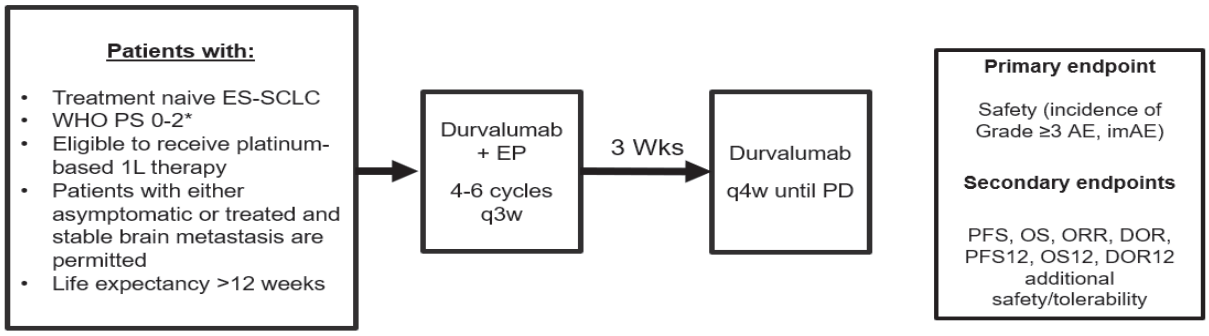
1.2 Study Design

This study is being conducted to evaluate the safety and tolerability profile of durvalumab plus platinum (cisplatin or carboplatin) plus etoposide (EP) in patients with ES-SCLC. An unmet need remains for additional safety and efficacy data to help support and inform treatment decisions on the use of durvalumab + EP for unselected patients in real clinical practice, including patients with Eastern Cooperative Oncology Group (ECOG) PS of 2, in combination with up to 6 cycles of chemotherapy and/or the use of PCI (Prophylactic cranial irradiation). Patients will receive durvalumab plus EP for up to 6 cycles (investigators choice, q3w) and then durvalumab q4w until PD.

The general study design is summarised in Figure 1

Figure 1 **Study design: A Phase IIIb, single-arm, multi-center, international study of Durvalumab in combination with platinum and etoposide for the first line treatment of patients with extensive-stage small cell lung cancer**



*PS2 limited to ≤30% ITT
N~150

Durvalumab 1500 mg, cisplatin (75-80 mg/m^2) or carboplatin (AUC5-6 [For PS2 patients a dose of AUC 4 is allowed]), etoposide (80-100 mg/m^2).

AE: adverse event; AUC: area under the curve; DoR: duration of response; DoR12: proportion of patients remaining in response 12 months from the time of first documented objective response; ES-SCLC: extensive-stage small-cell lung cancer; EP: platinum (cisplatin or carboplatin) plus etoposide; imAE: immune-mediated adverse event; OS: overall survival; OS12: proportion of patients alive at 12 months from first date of treatment; PFS: progression-free survival; PFS12: proportion of patients alive and progression-free at 12 months from first date of treatment; PD: Progression of disease; qXw: Every X weeks; PS: performance status; WHO: World Health Organization.

Approximately 150 patients will be treated with the study drug in North America and Europe. Patients must have histologically- or cytologically-documented ES-SCLC and be treatment naïve. Patients must be deemed to be eligible for etoposide and platinum-based chemotherapy per Investigator assessment.

1.2.1 Study Treatment

All patients will receive durvalumab 1500 mg administered via intravenous (IV) infusion concurrently with platinum-based chemotherapy (Investigator's choice of cisplatin or carboplatin) and etoposide q3w starting on Week 0 for up to 6 cycles. Durvalumab monotherapy will be continued q4w post-chemotherapy until confirmed radiological disease progression.

Unless specific treatment discontinuation criteria are met, patients enrolled will continue durvalumab therapy until confirmed radiological disease progression, unless there is clinical progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion

is met, as per investigator assessment.

EP will be administered for up to 6 cycles for patients per investigator clinical decision.

For Durvalumab, Dose delays are permitted for IO (Immuno-Oncology) therapy (see CSP Section 8.4.4 and Toxicity Management Guidelines in Annex to the Protocol). However, dose reduction is not permitted.

Dose modifications for EP will be performed according to local guidance.

The procedures for the screening and treatment periods in this study are presented in clinical study protocol.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw to occur at the timepoints indicated in the schedules of activities (SoAs). Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw to occur at the timepoints indicated in the SoAs.

For Durvalumab

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (TMG), due to either an immune or a non-immune-related adverse event (AE). In the event that durvalumab is discontinued or delayed as part of the toxicity management guidance, EP (platinum [cisplatin or carboplatin] plus etoposide) should still be administered as scheduled.
  - 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 (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]) and CCI assessments.

For Chemotherapy (Platinum [Cisplatin or Carboplatin] plus Etoposide [EP])

- 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. In the event that EP is delayed, durvalumab should also be delayed and to be resumed as soon as feasible. Every effort should be made to ensure patients receive at least 4 cycles of EP, if conditions allow.

1.2.2 Tumor Response Assessments

Tumor assessments using computed tomography (CT) or magnetic resonance imaging (MRI), each preferably with IV contrast, will be performed at the times specified in the schedule of assessment (Appendix A). RECIST 1.1 guidelines will be used to derive the secondary variables of PFS, OS, ORR, and DoR. The categorization of objective tumor response assessment into complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or not evaluable (NE) will be based on RECIST 1.1.

1.2.3 Overall Survival Assessments

All patients will be followed for survival until the end of the study.

Assessments for survival must be made as shown in Appendix A. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician.

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

The survival status (including cause of death) and the date of death or last follow-up date will be collected.

1.3 Number of Subjects

This is a safety study and no formal sample size calculation was done. However, a total of approximately 150 patients will be treated with durvalumab with platinum (cisplatin or carboplatin) plus etoposide. A maximum of 30% of all patients treated will have ECOG performance status of 2 at baseline. Assuming a CTCAE grade ≥ 3 incidence rate of 70%, approximately 150 patients are needed to achieve a precision no wider than 7.6% around the true incidence rate (based on Clopper-Pearson exact method). For this study, incidence rate is defined as

$$incidence\ rate = \frac{number\ of\ events}{number\ of\ subjects\ in\ the\ safety\ analysis\ set}$$

In addition, assuming an imAE incidence rate of 20%, the precision will be no wider than 6.7% around the true incidence rate. An illustration of the precision around the varying incidence rates of CTCAE grade ≥ 3 or imAE are provided in Table 1.

Table 1 Precision around varying incidence of AE

Precision of estimates of grade ≥ 3 AEs or imAE for Sample Sizes using Exact Binomial 95% CI				
Sample size	**True rate of grade ≥ 3 AE or imAE (%) and 95% CI**			
	20%	25%	60%	70%
150	**±6.7** 13.9 – 27.3	**±7.3** 18.6 – 33.1	**±8.1** 51.7 – 67.9	**±7.6** 62.0 – 77.2

AE: adverse event; CI: confidence interval: imAE: immune-mediated adverse event.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

With the exception of some summaries of patient disposition and particular individual patient data listings, which will be produced for all patients who provided informed consent and who were enrolled in the study, the Safety Analysis Set (SAF) will be used for listings, summaries, and analyses in the study.

The Enrolled Analysis Set will include all patients who signed informed consent.

The SAF will consist of all enrolled patients who received at least 1 dose of any study treatment.

The safety analysis set will be used for the efficacy analysis set.

2.2 Protocol Deviations

2.2.1 Important Protocol Deviations

According to ICH E3 guidelines version dated 1995 (ICH 1995),

> "Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety or well-being."

For this study, the following 7 general categories will be considered IPDs and will be summarized in the CSR:

- Deviation 1: Patients who received treatment and who deviated from the following key entry criteria in CSP:

- Inclusion Criterion 5: Histologically- or cytologically-documented ES-SCLC (stage IV [T any, N any, M1a/b], or with T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan, according to American Joint Committee on Cancer Stage 8th edition).
- Inclusion Criterion 6: Patients must be considered suitable to receive a platinum-based chemotherapy regimen as 1st line treatment for the ES-SCLC. Chemotherapy must contain either cisplatin or carboplatin in combination with etoposide.
- Inclusion Criterion 7: WHO/ ECOG Performance Status of 0 to 2 at enrollment.

  Note: Patients with PS2 will be limited to a maximum of 30% of the total study population; once this limit is met, additional enrolled patients must have PS 0-1.
- Inclusion Criterion 9: No prior exposure to immune-mediated therapy including, but not limited to, other anti- CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.
- Exclusion Criterion 1: History of allogeneic organ transplantation.
- Exclusion Criterion 3: Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- Exclusion Criterion 7: Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B virus (HBV) (known positive HBV surface antigen [HBsAg] result), hepatitis C virus (HBC), or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Exclusion Criterion 10: Received prior systemic therapy for ES-SCLC.

  Patients who have received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle from diagnosis of ES-SCLC.
- Exclusion Criterion 11: Medical contraindication to platinum (cisplatin or carboplatin)-etoposide-based chemotherapy.
- Exclusion Criterion 12: Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

- Exclusion Criterion 16: Patients who have received prior anti-PD-1 or anti PD-L1:
  - Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.
  - All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.
  - Must not have experienced a Grade $\geqslant$ 3 immune-related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. Note: Patients with an endocrine AE of Grade $\leqslant$ 2 are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.
  - Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.
- Exclusion Criterion 17: 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 (eg, intra articular injection).
  - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
  - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

- Deviation 2: Baseline Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 scan 42 days before enrollment. Note that the 42 days is based upon a 28-day screening period plus 2 weeks allowance so that only serious violators are identified.
- Deviation 3: No baseline RECIST 1.1 assessment on or before date of enrollment.
- Deviation 4: The patient met discontinuation criteria but did not discontinue investigational medicinal product (IMP) (eg, patient withdrew consent, patient became pregnant).
- Deviation 5: The patient received a prohibited concomitant medication or procedure as detailed in Section 6.4 of the CSP or any other concomitant medication or procedure which, upon physician review of all medications and procedures prior to database lock (DBL), is considered to have a potential effect on study outcomes.
- Deviation 6: Missed visits, assessments, or treatments that, in the opinion of the principal investigator, were due to COVID-19 global pandemic and where there was a significant effect on either completeness, accuracy, and/or reliability of the patient's data, or the patient's rights, safety or well-being.

- Deviation 7: Deviation from Good Clinical Practice (GCP) as determined by medical review.

2.2.2 Monitoring of Important Protocol Deviations

Programmable protocol deviations will be detected from the data recorded in the clinical database. The deviations will be reviewed and assessed on a case-by-case basis by AstraZeneca at monthly protocol deviation review meetings to determine importance of the deviation.. At this meeting, the programmatically-derived protocol deviations will be checked to ensure that they have been correctly classified as major or minor protocol deviations.

On an ongoing basis throughout the study, monitoring notes or summaries will also be reviewed to determine any important post entry deviations that are not identifiable via programming.

If the number of other deviations which are considered to have the potential to impact the primary analysis is considered important, sensitivity analyses may be performed on subgroups. This will be decided during the data review meeting and decisions will be documented prior to the soft database lock for primary analysis.

The final classification of IPDs will be made prior to database lock or data cut-off for final analysis. Deviations considered to be important will be listed and discussed in the CSR as appropriate. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3. ANALYSIS VARIABLES

3.1 Safety Variables

Safety and tolerability will be assessed in terms of AEs (including Grade ≥ 3 AE, imAEs, SAEs, AESIs, AEs resulting in treatment discontinuation, deaths, physical examinations, laboratory data, vital signs, ECGs, WHO/ECOG performance status and exposure). These will be collected for all patients throughout the study.

3.1.1 Primary Safety Endpoint

The primary endpoint of this study is the incidence of Grade ≥ 3 AE and incidence of imAEs. Any AEs which started after the 90th day following discontinuation of IMP will be included in the data listings. Any AE that occurs after the start of subsequent anti-cancer therapy will be flagged in the data listings. These events will not be included in AE summaries.

3.1.2 Secondary Safety Endpoints

The secondary safety endpoints of this study include:

- Treatment-emergent adverse events (TEAEs) and SAEs
- AESI (see Section 3.1.3.1)

- AEs leading to death
- AEs leading to study drug interruption or discontinuation
- Death from all causes
- Laboratory data including clinical chemistry, hematology, and urinalysis
- Physical Examination
- Vital signs including blood pressure, pulse, temperature, and respiration rate
- ECG

3.1.3 Adverse Events

Details of all AEs and SAEs will be collected for a patient from the signing of the informed consent form (ICF) until the follow-up period is completed (90 days after the last dose of durvalumab). 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.

All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) providing the System Organ Class (SOC) and Preferred Term (PT).

In addition, all AEs will also be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE Version 5.0) allocating grades from Grade 1 to Grade 4 which will be used for the reporting. The meaning of these categories are as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

TEAEs are are defined as events present at baseline that worsen in intensity after administration of IMP or events absent at baseline that emerge after administration of IMP, for the period extending to 90 days after the last dose of IMP. Any TEAE will be included in the AE summaries as detailed in Section 4.5.1.

Missing start and stop dates for AEs will be imputed using the rules described in Section 4.1.4.

3.1.3.1 Adverse Events of Special Interest

An 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 IMP. All AESIs will be programmatically derived.

An AstraZeneca medically qualified expert, after consultation with the Global Patient Safety Physician, will review all AEs of interest and identify which PTs contribute to each AESI. A further review will take place prior to DBL to ensure any further terms not already included are captured within the categories. The final list of PTs for all AESIs will be completed before DBL and documented in the Study Master File.

Time to event analyses for AESIs will be performed for the following definitions:

- Time to first onset of AESI: Start date of first AESI episode – First dose date of durvalumab + 1
- Time to first onset of AESI of Grade 3 or 4: First date of AESI episode that had CTCAE Grade 3 or 4 – First dose date of durvalumab + 1
- Time to resolution of AESI: End date of AESI episode – Start date of AESI episode + 1
- Time to resolution of Grade 3 or 4: End date of AESI episode that had CTCAE Grade 3 or 4 – First date AESI episode had severity of grade 3 or higher + 1

If an AESI does not resolve, then the time to resolution will be censored at earliest date of DCO, death date, or last dose date + 90 days. Patients who die prior to resolution of the AESI will be censored at the date of death.

3.1.3.2 Immune-Mediated Adverse Event

An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA 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. Adjudication of the imAEs will be performed by AstraZeneca using imAE charter.

Time to event analyses for imAEs will be performed for the following definitions:

- Time to first onset of imAE: Start date of first imAE episode – First dose date of durvalumab + 1
- Time to first onset of imAE of Grade 3 or 4: First date of imAE episode that had CTCAE Grade 3 or 4 – First dose date of durvalumab + 1
- Time to resolution of imAE: End date of imAE episode – Start date of imAE episode + 1
- Time to resolution of Grade 3 or 4: End date of imAE episode that had CTCAE Grade 3 or 4 – First date imAE episode had severity of grade 3 or higher + 1

If an imAE does not resolve, then the time to resolution will be censored at earliest date of DCO, death date, or last dose date + 90 days. Patients who die prior to resolution of the imAE will be censored at the date of death.

3.1.4 Electrocardiograms

These measurements are recorded as detailed in the study schedule (See Appendix A). Whenever ECGs, vital signs, 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.

At Screening, and as clinically indicated throughout the study, ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, including a corrected QT interval using Fridericia's formulae (QTcF) value > 470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

The QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

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

3.1.5 Vital Signs

Vital signs measurements will be collected at the start of each treatment cycle as detailed in the schedule of assessment (Appendix A).

Measurements will include SBP (mmHg), DBP (mmHg), pulse rate (breaths/min), weight (kg), body temperature (degrees Celsius), and respiratory rate (breaths/min). Height is recorded at screening only.

3.1.6 Laboratory Data

Laboratory data (clinical chemistry, haematology and urinalysis) will be collected at the start of each treatment cycle as detailed in the schedule of assessment and as clinically indicated (Appendix A). Coagulation tests are only performed at baseline on Day 1 (unless performed within 3 days prior to Day 1) and as clinically indicated. Laboratory data will be from local laboratories and will be converted to AZ preferred units, and AZ project reference ranges will be used for the primary interpretation of laboratory data.

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

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – Albumin (G/L)] × 0.02)

3.1.7 Physical Examination

Physical examinations will be performed according to the assessment schedules (Appendix A). Findings in these data will be reported as medical history at Screening and as AEs at post-screening visits and will be included in data analyses accordingly.

3.1.8 Exposure to IMP

The total (or intended) exposure (weeks) of IMP is defined as:

- Total treatment duration (weeks) = Total treatment duration (days) / 7

where:

Treatment duration (days) during durvalumab + EP treatment period = [earliest of (last dose date where dose > 0mg + 20 days, death date, cut-off date [DCO])-first dose date of durvalumab + EP] +1

Treatment duration (days) during durvalumab monotherapy period = [earliest of (last dose date where dose > 0mg + 27 days, death date, cut-off date [DCO])-first dose date of durvalumab monotherapy] +1

Total treatment durations (days) = treatment duration during durvalumab + EP treatment period + treatment duration during durvalumab monotherapy period

The actual exposure (weeks) of IMP is defined as:

- Actual treatment duration (weeks) = [total treatment duration (days) – total duration of dose delays (days)] / 7.

Dose reductions are not permitted per the CSP for durvalumab and the actual exposure calculation makes no adjustment for any dose reductions that may have occurred. If a patient's weight falls to 30 kg or below, the patient should receive weight based dosing equivalent to 20 mg/kg of durvalumab until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg.

Dose modifications for EP treatment can be performed according to local guidance.

Patients are scheduled to receive 1500 mg via IV infusion concurrently with platinum-based chemotherapy (Investigator's choice of cisplatin or carboplatin) and etoposide every 3 weeks (21 days) starting on Week 0 for up to 6 cycles. Durvalumab monotherapy will be continued every 4 weeks (28 days) post-chemotherapy until confirmed radiological disease progression. The duration of dose delays is the sum of all individual dose delays as follows:

- Duration of dose delays (days) during durvalumab + EP treatment period = sum of MAX[0, (date of dose [x+1] – date of dose [x] - 21 days)].

- Duration of dose delays (days) during durvalumab monotherapy period = sum of MAX[0, (date of dose [x+1] – date of dose [x] - 28 days)].

- Total duration of dose delays (days) = duration of dose delays during durvalumab + EP treatment period + duration of dose delays during durvalumab monotherapy period

If no delays were encountered, the total duration of dose delays would sum up to 0.

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation.

RDI is defined as follows:

RDI = 100% * d/D, where d and D are, respectively, the actual and intended cumulative doses delivered up to the date of durvalumab discontinuation or progressive disease or the data cut-

off date, whichever occurs earlier. D is the total dose that would be delivered if there were no modification to dose or schedule.

When deriving actual dose administered the volume before and after infusion will also be considered.

To illustrate the calculation of RDI, Table shows an example of durvalumab dosing for 4 patients.

Table 1 Example dose intensity scenarios

		Study Day									
RDI	Patient	1	29	43	64	85	106	134	155	176	181
100%	1	X	X	X	X	X	X	X	X	X	PD
100%	2	X	X	X	X	X	X	X	X[D]		PD
56%	3	X		X		X	O	X	X		PD
67%	4	X	X	O	X	X	X	O	X	O	PD

X: Dose of 1500mg taken; O: Dose missed; [D]: Dose discontinued; PD: Progressive Disease

In this example, all 4 Patients progressed on Day 181, and so the intended dose through to progression was 9 * 1500mg of durvalumab = 13500mg (13.5g).

Patient 1 received a total of 13.5g of durvalumab, whereas other patients received less durvalumab due to:

- Early stopping prior to PD (Patient 2)
- Dosing delays (Patient 3)
- Missed doses (Patient 4)

For RDI the examples of Patients 2 and 4 illustrate that the end of actual dosing period is calculated based on the smallest recovery period after the last non-zero dose.

Patient 1: RDI = (9 * 1.5g)/ 13.5g = 100%

Patient 2: RDI = (8 * 1.5g)/ 12g = 100%

Patient 3: RDI = (5 * 1.5g)/ 13.5g = 56%

Patient 4: RDI = (6 * 1.5g)/ 13.5g = 67%

Exposure will also be measured by the number of cycles (doses) of durvalumab received. If a cycle is prolonged due to toxicity this will still be counted as one cycle. A cycle will be counted if treatment is started, even if the full dose is not delivered.

3.2 Efficacy Variables

All RECIST assessments, whether scheduled or unscheduled, and regardless of whether a

patient discontinues durvalumab treatment or receives another anti-cancer therapy will be included in the calculation of efficacy variables.

3.2.1 Derivation of RECIST Visit Responses

This study will evaluate the efficacy of durvalumab + EP as secondary endpoints, in terms of OS, as well as PFS, PFS12, ORR, DoR, and DoR12, which will be derived from site Investigator assessments per RECIST1.1.

Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands), collected during screening/baseline and at regular (follow-up) intervals during study treatment. Tumor assessments from CT or MRI of the brain scan will be collected at baseline and when clinically indicated. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Treatment continues until clinical progression/deterioration or confirmed radiological progression, and scanning/tumor assessments continue throughout treatment until RECIST 1.1-defined radiological progression plus an additional follow-up scan (if clinically feasible).

The RECIST 1.1 guidelines provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and Non-Target Lesions (NTLs). -On-study images are evaluated for TLs and NTLs chosen at baseline, and for New Lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall timepoint responses (CR, PR, stable disease, PD, or Not Evaluable [NE]).

For all patients who are treated through progression, a follow-up scan is to be collected 4-8 weeks after the initial RECIST 1.1-defined PD; this follow-up scan is evaluated using the post-progression criteria outlined in CSP Appendix F. If the subsequent scan confirms the immediate prior radiological PD, no additional scans are required unless the patients are allowed to continue study treatment; however, if the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined PD which in turn will require a subsequent scan evaluated using the post-progression criteria outlined in Appendix F of CSP.

3.2.2 Progression-Free Survival

Progression-free survival is defined as the time from the first date of treatment until the date of objective disease progression as per RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from IMP or receives another anticancer therapy prior to progression.

- PFS (months) = (Date of event or Censor date – treatment start date +1) / (365.25/12)

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 assessment (ie, this doesn't include NE or missing value).

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 assessment prior to the 2 missed visits.

Given the scheduled visit assessment scheme (i.e. six-weekly for the first 12 weeks then eight-weekly thereafter) the definition of 2 missed visits will change.

1. If the previous RECIST assessment is baseline then two missing visits will equate to 13 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 6 weeks + 1 week for a late assessment = 13 weeks).
2. From week 13 onwards (when the scheduling changes to eight-weekly assessments), two missing visits will equate to 18 weeks (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks).

If the patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1 unless he/she dies within 2 visits of baseline, in which case the date of death is the event date.

If the patient has confirmed/suspected COVID-19 deaths, and has not progressed prior to death, he/she will be censored at the time of the latest evaluable assessment prior to the COVID-19 death date.

A sensitivity analysis will be conducted to assess for the potential impact of COVID-19 deaths on PFS. This will be assessed by repeating the PFS analysis except that any patient who had a PFS event due to death where primary/secondary cause of death was due to COVID-19 Infection, or a COVID-19 infection reported as a fatal AE, will be censored at their last evaluable assessment prior to their COVID-19 infection death date.

3.2.3 Overall Survival

The OS is defined as the time from the first date of treatment until death due to any cause.

- OS (months) = (Death date or Censor date - treatment start date +1) / (365.25/12)

Any patient who has confirmed/suspected COVID-19 death, or 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.

The date that an individual patient was last known to be alive will be identified exclusively using the data recorded within the SURVIVE and DEATH modules of the electronic case report form (eCRF).

A sensitivity analysis will be conducted to assess for the potential impact of COVID-19 deaths on OS. This will be assessed by repeating the OS analysis except that any patient who had a death with primary/secondary cause as COVID-19 Infection, or a COVID-19 infection reported as a fatal AE will be censored at their COVID-19 infection death date.

3.2.4 Objective Response Rate

The ORR is defined for the SAF as follows:

- The ORR is the proportion (%) of patients with an overall response of CR or PR based on Investigator-assessed response.

Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of the ORR. Responses that occur after the start of subsequent anti-cancer therapy must be excluded from the derivation of ORR (ie, only responses that occur prior to receiving subsequent therapy will be included in the numerator).

3.2.5 Best Objective Response

Best objective response (BoR) is the best response a patient has had after Day 1 up until progression, or the last evaluable assessment in the absence of progression. Responses that occur after the start of subsequent anti-cancer therapy must be excluded from the derivation. Categorization of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 6 weeks minus 1 week, ie, at least 35 days (to allow for an early assessment within the assessment window), after durvalumab initiation. For CR/PR, the initial overall visit assessment that showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs <= 7 weeks (ie, 6 weeks + 1 week to allow for a late assessment within the assessment window) after durvalumab initiation, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs > 7 weeks after Day 1 then BoR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time following Day 1, prior to RECIST progression and prior to starting any subsequent cancer therapy.

3.2.6 Duration of Response

For patients who are classified as responders (see Section 3.2.4), the DoR is 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.

- DoR (months) = (Date of PFS event or censoring – Date of start of response +1) / (365.25/12)

The date of the end of response should coincide with the date of disease progression or death from any cause used for the PFS endpoint (see Section 3.2.1). If a patient does not progress following a response, then the patients' DoR will be censored at the PFS censoring time.

3.3 CCI

CCI

3.3.1 CCI

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3.3.1.2 CCI [redacted]

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CCI [redacted]

3.3.2 WHO/ECOG Performance Status

WHO/ECOG PS will be assessed at the times specified in the schedule of assessments (Appendix A) 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 (eg, light housework or office work)

2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours

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

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

5. Dead

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

3.3.3 CCI

CCI [redacted]

CCI [redacted]

3.4 Other Variables

3.4.1 Baseline Characteristics

Baseline characteristics that will be collected or derived are:

- Demographics: age (years), sex, race and ethnicity.
- Patient characteristics: weight, height, body mass index (BMI).
- Medical history: name of past and/or concomitant diseases (verbatim and coded using the latest or current version of the MedDRA dictionary), start and stop dates.
- Nicotine use: smoking status (current, former, never), substance use name and pack years.
- Extent of disease upon entry of study: evidence of disease (yes/no), sites of metastatic/locally advanced disease, recent progression (yes/no, date), patients ES-SCLC progressing at enrolment (yes/no), reason tumor not amenable for resection.
- Previous cancer therapy: Number of prior chemotherapy regimens, number of cycles, therapy class, time from completion of chemotherapy to study treatment, best response to previous chemotherapy, treatment status, concomitant radiotherapy (yes/no).
- Previous radiotherapy: Total dose, radiotherapy site, time from completion of radiotherapy to study treatment, treatment status, concomitant chemotherapy (yes/no).
- Relevant surgical history: surgical procedure (verbatim and coded using the latest or current version of the MedDRA dictionary) and date of surgery.

- Characteristics of disease under investigation at diagnosis: original diagnosis date, primary tumor location, histology type, virology status at screening, macrovascular invasion (yes/no), extent of resection, primary tumor, American Joint Committee on Cancer (AJCC) staging.

3.4.2 Prior and Concomitant Medications and Therapies

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study will be recorded in the CRF. Details include generic and/or brand names of medications, WHO drug dictionary encoding, therapy reason, route, dose, dosing frequency, and start and stop dates.

Prior therapies are defined as those with at least one dose/treatment taken before the date of the first dose of IMP.

Concomitant therapies are defined as those with at least one dose/treatment taken between the date of first dose (inclusive) and the date of last dose (inclusive) of IMP.

Missing start and stop dates for medications will be imputed using the rules described in Section 4.1.4.

4. ANALYSIS METHODS

4.1 General Principles

4.1.1 General Statistical Considerations

The following general statistical considerations will be applied for the analyses and presentation of the data. In case of any specific deviations, methods will be specifically noted on the relevant output.

- The primary analysis, for safety, will be conducted approximately 6 months after the last patient is enrolled into the study and the final statistical analysis will be conducted after the last patient has had the opportunity to be followed up for a minimum of 12 months or 60% OS maturity, whichever occurs first. All the safety analysis will be done initially at 6 month and then same will be repeated at the final analysis.
- All data, demography, baseline characteristics, safety, efficacy and biomarkers, will be summarized using descriptive statistics, as appropriate for the type of data, for the SAF.
- Continuous variables will be summarized by the number of observations (n), mean, standard deviation, median, quartiles (Q1 and Q3), minimum, and maximum.
- For the continuous data, the summary statistics will be displayed with the following accuracy (number of decimal places):
    - The minimum and maximum with same accuracy as the raw data.
    - The mean, median and quartiles (Q1 and Q3) will be rounded to 1 additional decimal

place more than the number of decimal places in the raw data.

  - The standard deviation will be rounded to 2 additional decimal places more than the number of decimal places in the raw data.
  - If the number of observation is 1, then only n will be displayed in the output. Other summary statistics will be displayed as NE.

- Categorical variables will be summarized by frequency counts and percentages for each category and percentages will be rounded to one decimal place. If the percentage is 100%, no decimal places will be displayed.
- As a default, percentages will be calculated using the number of patients in the SAF as the denominator, with the exception of some summaries of patient disposition and particular individual patient data listings. If the denominator is different from this default, it will be explained in a footnote to the output.
- SAS® version 9.3 or higher will be used for all analyses.
- Exact CIs for proportions will be calculated using the Clopper-Pearson method.
- For percentiles of survival times based on the Kaplan-Meier method (eg, median PFS, median OS), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, the Klein and Moeschberger extension of the Brookmeyer-Crowley method).
- For point-estimates of survival based on the Kaplan-Meier method (eg, for PFS, OS), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, using Greenwood's estimate of standard error and a log-log transformation).
- The data will be included in summaries/analyses using the following criteria:
  - All laboratory data, vital signs data that are recorded at unscheduled visits will be included in the summaries using the visit windows defined in Section 4.1.5.1.
  - The tumor measurements should not be affected by any delays in treatment cycles/dates of start of treatment cycles as it is intended that they are only recorded at pre-scheduled time points. These data will be included in the summaries and analyses of the data using the visit windows defined in Section 4.1.5.2.
- All data collected including scheduled, delayed and unscheduled data will be listed in the patient data listings which are produced for all enrolled patients. They will be ordered by centre, WHO/ECOG PS group, patient and visit and, if relevant, timepoint when they were recorded. Patients who are included in the SAF will be flagged.
- All adverse events will be coded using MedDRA and NCI CTCAE Grade and will be reported using SOC and PT, NCI CTCAE Grade, as appropriate.
- All concomitant and previous medications will be coded using WHO drug dictionary and will be reported using anatomical therapeutic chemical (ATC) classification and generic term.

- Baseline is defined as the last assessment of the variable under consideration prior to the first dose of IMP regardless of whether the assessment is on Day 1, Screening or unscheduled. For RECIST and ECOG, baseline assessment will be on or before the first dose of IMP.
- All the outputs will be presented by ECOG PS 0 or 1 and ECOG PS 2.

4.1.2 Subgroup Analysis

All efficacy and safety data and some selected relevant data (eg, patient disposition, demography and baseline characteristics) will be summarised separately but not limited to the following subgroup:

- Age at baseline (<65 versus ≥65 years)
- Region
- CCI

4.1.3 General Considerations for Summary of Safety Data

The following considerations are for the summary of safety data.

- The missing values in vital signs, laboratory data, coagulation and urinalysis will not be imputed.
- If a laboratory value is reported as <LLQ (where 'LLQ' is the lower limit of quantification), then LLQ value will be used to impute '<LLQ' for the summary tables. In the data listings, this value will be listed as reported <LLQ.
- Any TEAEs with missing causality data will be considered as related to the durvalumab.
- Any TEAEs with missing assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels into CTCAE grades should be used. If severity is missing, the worst case will be assumed.
- Any partial dates will be presented as reported in the data listings. The partial dates will be imputed for the derivation of time to resolution, time to onset etc. using the criteria given in Section 4.1.4.

4.1.4 Handling of Missing Data

Missing safety data will generally not be imputed. However, safety assessment values of the form of "<LLQ" (ie, below the lower limit of quantification) or >ULQ (where 'ULQ' is the upper limit of quantification) will be imputed as the LLQ value or ULQ value in the calculation of summary statistics but displayed as "<LLQ" or ">ULQ" in the listings.

If the start date of the concomitant medication or AE is missing, the following rules will be applied:

- If the year is missing, the year should be imputed as the year that patient received the first dose of durvalumab.
- If the year is available and the month and day are missing, then impute the month as January and the day as 01.
- If the year and month are available and the day is missing, impute the day as 01 (the first day of the month).
- If any of the above puts the date before the date of first dose of durvalumab, a conservative approach is followed and, the date is imputed using the date of first dose.

If the stop date of the concomitant medication or AE is missing, the following rules will be applied:

- If the year is missing, the year should be imputed as the year that patient received the last dose of durvalumab.
- If the year is available and the month and day are missing, then impute the month as December and the day as 31.
- If the year and month are available and the day is missing, impute the day as the last day of the month (eg, 28, 29, 30 or 31).
- If any of the above puts the date after the date of the last dose of durvalumab, a conservative approach is followed and, the date is imputed using the data cut-off date (DCO).
- It is not expected to have missing dates for unscheduled laboratory, diagnostics data. However, if there are missing dates, for any derivations, the dates should be imputed following the rules for concomitant medications and AEs

4.1.5 Definitions of Visit Windows

Time windows are defined for all summaries of vital signs, laboratory data, CCI around visits in Section 4.1.5.1 and for tumor assessments around the scheduled RECIST assessment time in Section 4.1.5.2.

4.1.5.1 Visit Windows for Safety CCI Assessments

The following conventions will apply for safety CCI data:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data will have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.

If an odd number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 0.5 day.

For example, if a patient receives durvalumab plus EP for 4 cycles and then durvalumab monotherapy, the visit windows for vital signs data are:

- Week 1; nominal day 1, visit window Day 1
- Week 3; nominal day 22, visit window 2 – 32
- Week 6; nominal day 43, visit window 33 – 53
- Week 9; nominal day 64, visit window 54 – 74
- Week 12; nominal day 85, visit window 75 – 98
- Week 15; nominal day 106, visit window 96 – 116
- Visits after treatment discontinuation will be assigned to the last treatment cycle for up to 15 days only. Visits after the 15 days will contribute to the following 30 days post treatment discontinuation interval, see below.

- Visits up to 90 days after last dose will be assigned similarly to the definition for the visits under treatment, but for 30 day intervals after treatment discontinuation, eg,:
  - 30 days after last dose, visit window 16 – 45
  - 60 days after last dose, visit window 46 – 75
  - 90 days after last dose, visit window 76 – 97
  - Data recorded after 97 days after last dose will not contribute to the analysis period of up to 90 days following the date of last dose, and will not be re-mapped
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded during treatment period will be used (regardless of where it falls in an interval), visits post treatment discontinuation will not be used.
- Listings should display all values based on the scheduled or unscheduled visit specified on the eCRF on which the data were collected for a patient.

For visit based summaries:

- If there is more than one value per patient within a time window then the closest value to the scheduled visit date should be used, or the earlier in the event the values are equidistant from the nominal visit date. If there are two values recorded on the same day and the parameter is CTCAE gradable then the record with the highest toxicity grade should be used. The listings should highlight the value for that patient that went into the summary table, wherever feasible. Note: in summaries of extreme values all on-treatment values collected are used including those collected at unscheduled visits.
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a patient level statistic such as a maximum.

4.1.5.2 Visit Windows for Tumor Assessments

The following conventions will apply for tumor assessment data:

- All tumor assessments available during the study should be used for the efficacy analysis. A windowing rule will be applied and will follow the CSP allowed visit window; therefore, any RECIST assessment performed within ± 1 week of the CSP scheduled visit will be used for that visit.
- If there are any assessments outside these visit windows, they will also be included in the closest visit window following the intent-to-treat principle. The tumor assessments which are outside the visit windows will be flagged in the data listings.

The above could result in more than one tumor assessments within a window and in that case, the one closest to the scheduled assessment will be used.

4.2 Study Population

4.2.1 Patient Disposition

The following patient disposition summaries will be produced:

- The number and percentage of patients who were screened, who were screening failures, and who received and did not receive IMP will be summarised for all patients.
- Discontinuation from durvalumab, discontinuation from EP , discontinuation from study, together with reason for discontinuation will be summarised for all patients.
- Discontinuation of study intervention and/or withdrawal from study due to COVID-19 will be presented separately.

The date and day of the last contact, date of informed consent, date of genetic informed consent, date of determining eligibility for the study, treatment completion status, study completion status will be listed in patient disposition listings.

The number and percentage of patients with confirmed or suspected COVID-19 infection will be presented separately, including details on COVID-19 related interruptions impacting on visits and investigational product administration. Listings of patients affected by the COVID-19 pandemic will be presented detailing any affect and impact on the study. Issues reported in the Clinical Trial Management System will be considered for presented in listings as well.

4.2.2 Protocol deviations

Important protocol deviations are defined in Section 2.2.1 and will be listed and summarized for the SAF, including a summary of those identified as resulting from the COVID-19 pandemic.

The number and percentage of patients with any IPD will be summarized for each IPD category. Patients with more than one deviation in the same IPD category will be counted once for that IPD category. Any patients who have deviations in more than one IPD category will be counted once in the overall summary.

4.2.3 Demography and Baseline Characteristics

Demographic and other baseline characteristics (see Section 3.4.1) will be listed for all patients and summarised for the SAF, as:

- Demographics (age, age group [<50, >=50-< 65, ≥ 65-<75, and ≥ 75 years], sex, race and ethnicity)
- Patient characteristics at baseline (height, weight, body mass index (BMI), and BMI groups [Underweight (<18.5), Normal weight (>=18.5 - <25.0), Overweight (>=25.0 - <30.0), Obese (>=30.0)], childbearing potential, menopausal status)
- Nicotine use and consumption (smoking status (current, former, never), pack years)
- Extent of disease upon entry of study (evidence of disease, sites of metastatic/locally advanced disease, recent progression [yes/no, date], patients ES-SCLC progressing at enrolment, reason tumor not amenable for resection)
- Characteristics of disease under investigation at diagnosis (original diagnosis date, primary tumor location, histology type, virology status at screening, macrovascular invasion, extent of resection, primary tumor, AJCC staging)
- Previous cancer therapy (number of prior chemotherapy regimens, number of cycles, therapy class, time from completion of chemotherapy to study treatment, best response to previous chemotherapy, treatment status, concomitant radiotherapy)
- Previous radiotherapy (total dose, radiotherapy site, time from completion of radiotherapy to study treatment, treatment status, concomitant chemotherapy)
- A summary and a list of patients by site and country will be provided.

Medical history and relevant surgical history are coded using MedDRA and will be summarized by SOC and PT.

If necessary, demographics will further be summarized separately for all patients in the SAF who had confirmed or suspected COVID-19 infection.

4.2.4 Previous and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be listed for all patients in the SAF.

Concomitant medications will be summarized by chemical subgroup (ATC 4th level), and preferred WHO name for the SAF. Patients with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than one chemical and/or therapeutic subgroups will be presented in each subgroup.

4.3 Analysis of Primary Safety Endpoint

The primary endpoint of this study is the incidence of Grade ≥ 3 AE and incidence of imAE. Any Grade ≥ 3 AEs or imAEs which started more than 90 days after discontinuation of IMP will not be included.

The number and percentage (and exact Clopper-Pearson 95% CI) of patients with NCI CTCAE Grade ≥ 3 AEs will be summarized for all patients in the SAF. The number and percentages of patients with NCI CTCAE Grade ≥ 3 AEs will also be summarized by SOC and PT. Same tables will be presented for patients with imAEs.

4.4 Analysis of Secondary Efficacy Endpoints

All statistical analyses of the efficacy endpoints will be presented using the SAF.

The tumor evaluation of target lesion and non-target lesion will be listed, and all tumor response will be listed.

Tumor size will also be presented graphically using waterfall plots, to present each patient's month 12 percentage change in target lesion tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. In this plot, the response status (CR, PR, SD, PD, or NE) will be distinguished.

4.4.1 Progression-Free Survival

Kaplan-Meier plots and descriptive statistics will be provided for PFS. Summaries will include number (%) of patients experiencing a PFS event, type of event (disease progression or death), number of patients censored, lower and upper quartile and median PFS (months), along with the 95% confidence interval. The 3-month (Day 92), 6-month (Day 183), 9-month (Day 274), 12-month (Day 365) PFS estimates will also be presented.

In addition, proportion of patients alive and progression-free at 12 months from the first date of treatment (PFS12) will be presented with the corresponding exact 95% CIs.

If necessary, a sensitivity analysis will be conducted to assess the potential impact of COVID-19 related deaths on PFS. That is, patients who had a PFS event due to death where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored at the last evaluable RECIST 1.1 assessment prior to COVID-19 infection related death.

4.4.2 Overall Survival

Kaplan-Meier plots and descriptive statistics will be presented for OS. Summaries will include number (%) of patients experiencing an OS event (overall and also at Month 12), type of event (death), number of patients censored, lower and upper quartile and median OS (months), along with the 95% confidence interval.

In addition, proportion of patients who are alive 12 months from the first date of treatment (OS12) will be presented with the corresponding exact 95% CIs.

If necessary, a sensitivity analysis will be conducted to assess the potential impact of COVID-19 related deaths on OS. That is, patients who had a death event where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored at the date of their COVID-19 infection related death.

4.4.3 Objective Response Rate

The ORR based on investigator-assessed response will be estimated for the SAF and will be presented with the corresponding exact 95% CIs.

The number (%) of patients with a CR or PR and the number (%) of patients with a single visit response (ie, an unconfirmed response) will also be presented.

4.4.4 Duration of Response

A Kaplan-Meier plot and descriptive statistics will be provided for the DoR for patients in the SAF who had responded to treatment (see Section 3.2.6). In the event of insufficient number of events, descriptive statistics will be provided. Summaries will include: number (%) of responders experiencing a PFS event (overall and also at Month 12), type of event (disease progression or death), number of patients censored, lower and upper quartile and median DoR with appropriate 95% CIs. The 3-month (Day 92), 6-month (Day 183), 9-month (Day 274), 12-month (Day 365) DoR estimates will also be presented.

In addition, proportion of patients who remain in response 12 months after first documented response (DoR12) will be presented with the corresponding exact 95% CIs.

Swimmer plots that clearly show the profile of each patient who responds will also be produced.

4.5 Analysis of Secondary Safety Endpoints

4.5.1 Adverse Events

All AEs reported up until 90 days following completion or discontinuation of durvalumab treatment or until the initiation of the first subsequent therapy (whichever occurs first) will be included in the summaries unless explicitly stated otherwise below.

All AEs will be summarised descriptively, in terms of number of patients (n) and percentage of patients (%) reporting the event by MedDRA SOC and PT.

Listings of AEs will include the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity, relationship to durvalumab, relationship to EP treatments, and NCI CTCAE Grade. Separate listings will be produced for all AEs, SAEs, AESIs, imAEs, AEs leading to treatment discontinuation, AEs leading to treatment interruption, AE leading to death. Listings of AESIs and imAEs will also include the additional information (eg, intervention, dose, duration of therapy etc.) recorded for these AEs. All AEs that are not treatment-emergent will be flagged in the data listings and the time of onset will be flagged as 'pre-treatment', 'post-treatment and no other anti-cancer therapy' and 'after initiation of other anti-cancer therapy'.

An overall summary of AE data will be presented including the number and percentage of patients reporting the following:

- At least one AE
- At least one AE of CTCAE Grade ≥ 3
    - Exact Clopper-Pearson 95% CI will be reported for patients overall and

separately by ECOG PS 0 to1 and PS 2

- At least one AE of CTCAE Grade ≥ 3, possibly related to durvalumab
- At least one AE of CTCATE Grade≥ 3, possibly related to EP (etoposide+platinum)
- At least one SAE
- At least one SAE, possibly related to durvalumab
- At least one SAE, possibly related to EP (etoposide+platinum)
- At least one AESI
- At least one imAE
    - Exact Clopper-Pearson 95% CI will be reported for patients overall and separately by ECOG PS 0 to1 and PS 2
- At least one AE leading to interruption or discontinuation of durvalumab
- At least one AE leading to interruption or discontinuation of EP (etoposide+platinum)
- (cisplatin/carboplatin)
- At least one AE leading to interruption or discontinuation of durvalumab, possibly related to durvalumab
- At least one AE leading to interruption or discontinuation of EP (etoposide+platinum), possibly related to EP (etoposide+platinum)
- At least one AE leading to death
- At least one AE associated with COVID-19

The following summaries including the number and percent of patients by SOC and PT, and maximum NCI CTCAE grade will be presented separately:

- All AEs
- All AEs of CTCAE Grade ≥ 3
- All SAEs
- All AEs leading to death
- All AEs leading to death, possibly related to study treatment
- At least one AE leading to interruption or discontinuation from study drug durvalumab
- At least one AE leading to interruption or discontinuation from EP treatments
- At least one AE leading to interruption from study drug durvalumab
- At least one AE leading to discontinuation from study drug durvalumab
- All AEs associated with COVID-19
- All AEs excluding AEs associated with COVID-19
- All confirmed/suspected COVID-19 AEs
- All AEs excluding confirmed/suspected COVID-19 AEs
- AEs leading to discontinuation of study intervention, excluding TEAEs associated with COVID-19 infection
- AEs associated with COVID-19 infection leading to discontinuation of study intervention
- AEs with outcome of death, excluding TEAEs associated with COVID-19 infection
- AEs associated with COVID-19 infection with outcome of death

If multiple AEs of the same PT occur within a patient, only the maximum grade observed for this PT will be used in summary of AEs by grade; the patient will be counted only once in the number of patients for this PT and only once for the number of patients for the SOC to which the PT belongs.

A summary of most common AEs and another summary of most common AEs with CTCAE Grade 3 or higher, including all events that occur >2.5% of patients overall will be presented by PT, by decreasing frequency. This cut-off may be modified after review of the data. The raw percentage will be compared to the cut-off, without applying any rounding to the percentage value (ie, a TEAE with frequency of 2.5% will not appear in the table if a cut-off is 2.5%). This summary will also be presented for patients who received <=4 cycles and >4 cycles of EP (etoposide+platinum) based on etoposide.

A separate data listing of AEs occurring more than 90 days after discontinuation of IMP, and a data listing of AE associated with COVID-19 will be produced.

A summary of deaths will be provided with the following information:

- Number of deaths (related to disease under investigation, non-related, and unknown)
  - Number of deaths during the on-treatment study period up until 90-day follow-up and prior to initiation of first subsequent therapy
  - Number of deaths occurring more than 90 days after the last dose of durvalumab or after initiation of first subsequent therapy

Listings of key patient information for Deaths and SAEs will be provided.

4.5.1.1 Adverse Events of Special Interest and Immune-Mediated Adverse Events

The following summaries of AESIs/AEPIs will be presented by AESI category and PT, seriousness, causality, maximum NCI CTCAE grade, and immune-relatedness:

- All AESIs/AEPIs
- All serious AESIs/AEPIs
- All AESIs/AEPIs leading to interruption or discontinuation from study drug durvalumab
- All AESIs/AEPIs leading to interruption or discontinuation from EP treatments
- All AESIs leading to death

Number and proportion of patients who received steroids, immunosuppressants, or hormone replacement therapy to manage AESIs will be summarized with the following time to event analyses for AESI/AEPI, by type of intervention:

- Time to first onset of AESI/AEPI
- Time to first onset of AESI/AEPI of Grade 3 or 4
- Time to resolution of AESI/AEPI
- Time to resolution of AESI/AEPI of Grade 3 or 4
- Duration of intervention with steroids, immunosuppressants, or hormone replacement therapy until the resolution of AESI/AEPI

Overall summaries will present the numbers and percentages of patients with at least one imAE by the following categories:

- imAE
- imAE of CTCAE Grade ≥ 3
- imAE leading to interruption or discontinuation from study drug durvalumab
- imAE leading to interruption or discontinuation from EP treatments
- imAE leading to death

Using the same categories above similar summaries will be presented by preferred term, and by SOC and PT.

Time to event analyses for immune-mediated AE (imAE) will be performed by AESI categories, for:

- Time to first onset of imAE
- Time to first onset of imAE of Grade 3 or 4
- Time to resolution of imAE
- Time to resolution of imAE of Grade 3 or 4

For patients with imAEs having multiple PTs within an AESI category the AEs will be collapsed to one event if the difference between end date of an imAE and subsequent start date of the next imAE is <=3 days. The time to onset will be based upon the first PT, whereas time to resolution used for KM analysis will be based on time of the worst imAE episode from that given patient. Summaries will include the number and percentage of patients with imAEs, lower and upper quartile and median time to event (days), and descriptive statistics.

At the AESI/AEPI grouped term level for time to resolution outputs the worst imAE is defined in the order of the following:

- imAE with worst (highest) grade first
- For more than one imAE with the same highest grade take imAE which did not resolve before imAE which did resolve
- If multiple imAE and all resolved take imAE with longest duration

Summaries for imAEs and related data will be presented by imAE category and PT:

- All imAE
- All serious imAE
- All imAEs by maximum CTCAE Grade
- All imAEs by outcome
- All imAEs leading to interruption or discontinuation from study drug durvalumab
- All imAEs leading to interruption or discontinuation from EP treatments
- All imAEs leading to death

4.5.2 Electrocardiograms

Summaries of absolute and change from baseline values of each ECG parameters will be presented by visit.

All individual ECG data will be listed.

4.5.3 Vital Signs

Absolute values and change from baseline for vital sign parameters (SBP, DPB, pulse rate, temperature, and respiration rate) will be summarised by visit.

Box plots of the vital signs results by visit will be presented.

4.5.4 Laboratory Data

Laboratory data obtained up until the 90 days after last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first) will be used for reporting.

Absolute values and change from baseline for all continuous haematology and clinical chemistry laboratory parameters will be summarised by visit. If a patient does not have the baseline value of laboratory data or the value at visit, the change from baseline is considered as missing.

Shift tables for laboratory values by worst CTCAE Grade will be produced. The laboratory parameters for which CTCAE Grade shift outputs will be produced are:

- Haematology: Absolute neutrophil count, Absolute lymphocyte count, Absolute leukocytes count, Hemoglobin, Platelet count, Total white cell count
- Clinical chemistry: Albumin, Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), Amylase, Bicarbonate, Calcium, Chloride, Creatinine, Gamma glutamyl transferase, Glucose, Lactate dehydrogenase, Lipase, Magnesium, Potassium, Sodium, Total bilirubin, Total protein, Urea or blood urea nitrogen (depending on local practice)

For categorical urinalysis parameters (Bilirubin, Blood, Glucose, Protein), a shift table will be produced comparing baseline value to maximum on-treatment value.

For the parameters with no CTCAE grading that are listed in the CSP the number and percentage of patients with laboratory values outside normal range will be summarized by

shift tables from baseline to the post-baseline maximum and minimum value on-treatment.

4.5.4.1 Hy's Law

The following summaries (n, %) of the laboratory data will be used to identify cases of Hy's law:

- Elevated ALT, AST, and total bilirubin during the study
  - ALT ≥ 3x – ≤ 5x, > 5x – ≤8x, > 8x – ≤10x, >10x – ≤20x and >20x upper limit of normal (ULN) during the study
  - AST ≥ 3x – ≤ 5x, > 5x – ≤8x, > 8x – ≤10x, >10x – ≤20x and >20x ULN during the study
  - Total bilirubin ≥2x – ≤3x, >3x – ≤5x, >5x ULN during the study
  - ALT or AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x and >20x ULN during the study
  - ALT or AST ≥3x ULN and total bilirubin ≥2x ULN during the study (Potential Hy's law): The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation

Narratives will be provided in the CSR for patients who have ALT ≥ 3x ULN plus Total bilirubin ≥ 2x ULN or AST ≥ 3x ULN plus Total bilirubin ≥ 2x ULN at any visit.

Liver biochemistry test results over time for patients with elevated ALT or AST (ie, ≥ 3x ULN), and elevated Total bilirubin (ie, ≥ 2x ULN) (at any time) will be plotted. Individual patient data where ALT or AST (ie, ≥ 3x ULN) plus Total bilirubin (ie, ≥ 2x ULN) are elevated at any time will also be listed.

Plots of post-baseline ALT and AST vs. post-baseline total bilirubin will also be produced with reference lines at 3×ULN for ALT, AST, and 2×ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Potential Hy's law will also be summarized by liver risk factor, occurrence (yes/no), reference period (before/ongoing), and duration. All individual liver risk factors data and liver diagnostic investigation data will be listed.

4.5.4.2 Assessment of Thyroid Function Test Results

Shift table for TSH test, baseline versus maximum value on treatment will be produced for the categories:

- Low
- Normal
- >1 to 2 x ULN
- >2 x ULN

The following summaries will include the number and percentage of patients who have elevated

or low TSH:

- On-treatment elevated TSH > ULN
- On-treatment elevated TSH > ULN with TSH <= ULN at baseline
- On-treatment elevated TSH > ULN
    - With at least one T3 free/ T4 free < LLN
    - With all other T3 free/ T4 free >= LLN
    - With T3 free/ T4 free missing
- On-treatment low TSH < LLN
- On-treatment low TSH < LLN with TSH >= LLN at baseline
- On-treatment low TSH < LLN
    - With at least one T3 free/ T4 free > ULN
    - With all other T3 free/ T4 free <= ULN
    - With T3 free/ T4 free missing

4.5.5 Physical Examination

Full physical examinations are to be collected at baseline only. By-subject listings will be provided.

All individual targeted physical examination data will be listed only.

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 unless unequivocally related to the disease under study.

4.5.6 Exposure

The following summaries will be presented for durvalumab exposure during durvalumab + EP treatment period, durvalumab monotherapy period, and overall:

- Total (or intended) exposure
- Actual exposure
- Number of cycles received
- Number and Reasons for dose delays of IMP
- Relative dose intensity

Same summaries will be presented for EP treatments exposure during durvalumab + EP treatment period.

Individual patient data for each study drug administration (durvalumab and EP treatments) will be listed for all patients in the SAF.

All overdose report will be listed.

All medical error reports will be listed.

4.5.7 Pregnancy Test

Positive pregnancy test results will be listed only.

4.5.8 Therapy following discontinuation from IMP

All recorded details of anti-cancer therapies subsequent to the discontinuation of IMP will be listed.

4.6 CCI

4.6.1 CCI

CCI

4.6.1.1 CCI

CCI

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CCI

CCI

- CCI
- CCI

4.6.1.2 CCI

CCI

CCI

4.6.2 CCI

CCI

CCI

4.6.3 CCI

CCI

5. INTERIM ANALYSES

The timing of the primary analysis of safety will be approximately 6 months after the last patient is enrolled into the study.

No formal interim analysis is planned for this study.

If required, a Steering Committee (SC) will be assembled by AstraZeneca for the executive oversight and supervision of the study. The SC may consist of oncology experts and a statistician who serve their role through regular scheduled meetings or teleconferences and, if necessary, additional ad hoc meetings. Details of the SC remit, procedures, processes, and meeting frequency will be outlined in an SC Charter.

An early safety review and early response will be performed based on the first 51 patients dosed who has had an opportunity to receive 6 cycles of chemotherapy+3days.

6. CHANGES OF ANALYSIS FROM PROTOCOL

"APF12" in the Protocol section 8.1 should be corrected as 'PFS12'.

Deleted United Kingdom as they are not participating in the study.

"Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab (see current Investigator Brochure [IB] for durvalumab)" was removed

from section 1.2.1, and will be removed from future CSP amendment. Because this sentence is inconsistent with Schedule of Assessments as the dosing is q3w +/- 3 days.

7. REFERENCES

CCI [redacted]

AJCC
The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM, Annual Surgical Oncology 2010.

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SAS
SAS/STATS® User Guide, Version 9.3, Cary, North Carolina, SAS Institute Inc.

8. APPENDIX

8.1 Appendix A: Schedule of Assessments

The schedule of assessment is mentioned in the clinical study protocol.

SIGNATURE PAGE

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