Clinical Study Protocol	
Drug Substance	Durvalumab
Study Code	D419BR00018
Version	2.0
Date	31 Mar 2021

An Open Label, Multicenter Study of First-Line Durvalumab plus Platinum-Based Chemotherapy in Chinese Patients with Extensive Stage Small-Cell Lung Cancer (Oriental)

Sponsor: AstraZeneca Investment (China) Co., Ltd

VERSION HISTORY

Version 2.0, 31 Mar 2021
• Removal of "exact" and add "using Clopper-Pearson method" to describe 95% CIs. Section updated: **Synopsis, Section 9.5.1** and **9.5.2**
• Addition of "or unacceptable toxicity" in study design and Table 2. Section updated: **Section 2.3, Table 2**
• Addition of inclusion criteria 8 and update of inclusion criteria 11. Section updated: **Section 4.1**
• Update information of "discontinuation of study treatment". Section updated: **Section 4.6**
• Update and delete the content not applicable. Section updated: **Section 4.7.1** and **4.7.2**
• Addition of "Cycle 1" at Baseline for clarity. Removal of Inclusion/exclusion criteria check at baseline. Update tumor assessment to clarify that patients who stops durvalumab treatment because of toxicity before PD will be required to continue tumor assessment during safety and survival follow-up period). Section updated: **Table 2**
• Removal of the paragraph "Note: For coagulation parameters, activated partial thromboplastin time [either as a ratio or as an absolute value, in seconds]and international normalized ratio are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and as clinically indicated". Section updated: **Table 4**
• Update the collection and follow-up of AEs and SAEs. Section updated: **Section 7.3.1** and **7.3.2.**
• Removal the section of "Reporting of Non-serious Adverse Drug Reaction (Non-serious ADR)". Section updated: **Section 7.5 (deleted)**
• Addition of the paragraph "The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 7.4) and within 30 days for all other pregnancies. The same timelines apply when outcome information is available." Section updated: **Section 7.7.1**
• Addition of the underline words "The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1

(initial fatal/life-threatening or follow up fatal/life-threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 7.8) and within 30 days for all other medication errors. The designated AstraZeneca representative will ensure a Medication Error Report Form is forwarded to site, completed and sent to AZ DES." Section updated: **Section 7.8** • Update of EP supply information. Section updated: **Section 8.1** • Addition of the underline words "Patients who continue to receive IP at the discretion of the Investigator can receive treatment until they are no longer deemed to be receiving clinical benefit or end of the study". Section updated: **Section 8.2.1** • Update the tumor response as "overall tumor response". Section updated: **Section 9.4.2** • Update the subgroup analysis. Section updated: **Section 9.5.3** • Minor administrative changes for clarification and to correct typographical errors
Version 1.0, 27 Dec 2019
Initial version

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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study clinical study protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
CD	Cluster of differentiation
CI	Confidence interval
CL	Calculated creatinine clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
C_{min}	Minimum plasma concentration
CR	Complete response
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DCO	Data Cut Off
DCR	Disease control rate
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
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor

Abbreviation or special term	Explanation
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPI	First patient in
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Council for Harmonisation Tripartite Guideline for Good Clinical Practise' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance).
GMP	Good Manufacturing Practice
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Hazard ratio
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
IC	Immune cell
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IP	Investigational product
IRB	Institutional Review Board, synonymous to Ethics Committee (EC) and Independent Ethics Committee (IEC)
IO	Immuno-oncology
IV	Intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
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
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
q3w	Every 3 weeks
q4w	Every 4 weeks
QC	Quality Control
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small-cell lung cancer
SD	Stable disease
SoC	Standard of care
sPD-L1	Soluble programmed cell death ligand 1
TC	Tumor cells
TL	Target lesion
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

1 PROTOCOL SYNOPSIS

An Open Label, Multicenter Study of First-Line Durvalumab plus Platinum-Based Chemotherapy in Chinese Patients with Extensive Stage Small-Cell Lung Cancer (Oriental)

Study site(s) and number of subjects planned

Approximately 300 extensive stage small-cell lung cancer (ES-SCLC) patients, who fulfil the inclusion/exclusion criteria, will be recruited by the investigational sites in China.

Study Period:	
Estimated date of first patient enrolled	Q3 2020
Estimated date of last patient completed	Q4 2022

Study design:

This will be an open-label, single-arm, multicenter, Phase IIIb study to determine the safety of durvalumab + etoposide and cisplatin or carboplatin as first-line treatment in patients with extensive stage small-cell lung cancer. Patients who fulfil all the inclusion criteria and none of the exclusion criteria will be enrolled and receive treatment with durvalumab + etoposide and either cisplatin or carboplatin (EP) for 4 to 6 cycles. Durvalumab will be administered at a dose of [redacted] with first-line chemotherapy (EP) and will continue to be administered as monotherapy every 4 weeks (Q4W) post-chemotherapy until progressive disease (PD) or intolerable toxicity. Prophylactic cranial irradiation (PCI) is allowed at the investigators' discretion as per SoC guidance for ES-SCLC. Patients will attend a safety follow up visit 90 days after last dose of durvalumab.

Objectives:

All objectives will be evaluated for all patients, unless otherwise indicated.

Primary objective:	**Endpoint/variable:**
To assess the safety and tolerability of durvalumab + EP in patients with performance status 0-2	Incidence of Grade ≥3 AE Incidence of imAE

AE Adverse event; EP Etoposide and platinum-based chemotherapy; imAE Immune-mediated adverse event.

Secondary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab + EP in terms of PFS, ORR and OS	PFS, APF12, ORR, DoR using site Investigator assessment and OS, OS12

To assess the safety and tolerability profile of durvalumab + EP	Incidence of AEs, SAEs, AESIs, AE resulting in treatment discontinuation

AESIs adverse event of special interest; DoR Duration of Response; EP Etoposide and platinum-based chemotherapy; ORR Objective response rate; OS Overall survival; OS12 Overall survival at 12 months after first dose of study treatment; PFS Progression free survival; APF12 Proportion of patients alive and progression free at 12 months after first dose of study treatment.

Target patient population

Adult patients (aged ≥18 years) with histologically or cytologically documented extensive stage SCLC (stage IV [T any, N any, M1 a/b/c], 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). Patients must have World Health Organization/Eastern Cooperative Oncology Group performance status of 0-2; patients with PS2 will be limited to 20% of the total study population.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients enrolled will continue durvalumab therapy until disease progression or intolerable toxicity, as per investigator assessment.
EP will be administered for 4 to 6 cycles for patients per investigator clinical decision.

Efficacy assessments

Tumour assessments will be performed as per RECISTv1.1 criteria, using computed tomography (CT)/magnetic resonance imaging (MRI). The baseline assessment is part of the screening procedures and should be performed before the start of study drug. Imaging assessment performed according to local standard clinical practice within 28 days before the first dose of study drug, but prior to signing the informed consent form (ICF), can be used for screening purposes if the patient consents to the use of those results. Efficacy for all patients will be assessed per investigator using objective tumour assessments according to RECIST v1.1 at week 6±2 weeks, week 12±2 weeks and Q8W ±2 weeks thereafter, until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping study drug and/or initiation of subsequent therapy). The schedule of imaging radiological assessments should be followed regardless of any dose delays.

The date, procedure, and overall response at each follow-up visit time-point will be documented, as well as if the patient is receiving benefit from the study medication. In case of disease progression, the physician will assess, date, and document the progression and methods (eg CT scan) used as per standard definitions and routine institutional standard of care.

Follow-up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity or symptomatic deterioration,

clinical progression, withdrawal from treatment, or patients who have started a subsequent anticancer therapy, will be followed up for survival.

Survival

All patients enrolled in the study should be followed up for survival until death, withdrawal of consent, or the end of the study.

Investigational product, dosage, and mode of administration

[redacted]

Statistical methods

A comprehensive Statistical Analysis Plan (SAP) will be prepared before FPI.

Approximately 300 patients will be enrolled to this study. All subjects who received at least 1 dose of study treatment will be included in the safety analysis set, which will be the primary analysis set for all analyses.

The primary objective of this study is to assess the safety and tolerability of durvalumab + EP, in terms of the incidence of Grade ≥3 AE and incidence of imAE. A secondary objective of this study is to further assess the safety and tolerability of durvalumab + EP, in terms of all AEs, SAEs, adverse events of special interest (AESI) and AEs leading to treatment discontinuation. Safety data will be summarized descriptively overall, by seriousness, by causality, and by maximum National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) grade (v5.0) based on the safety analysis set. Continuous variables will be summarised by the number of observations (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. The Clopper-Pearson 2-sided 95% CIs around incidence will also be reported for Grade ≥3 Aes, for each imAE, and where appropriate, for other AE types.

The efficacy of first-line durvalumab + EP will be assessed as secondary objectives, in terms of PFS, APF12, ORR, DoR, OS, OS12. Time-to-event data will be summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% CIs; data will be reported for patients overall and separately for patients based on performance status (0 to 1

and 2). ORR (based on Investigator assessment) will be summarized descriptively, and the 95% confidence intervals (CIs) using Clopper-Pearson method will be reported.

As the safety of durvalumab + EP has not been previously established in ES-SCLC patients with PS2, a safety review committee (SRC) will be established to review the safety and tolerability data of the combination of Durvalumab+EP in this subset of patients at an early stage of enrolment. SRC will include AZ local study team member such as study physician, MC PV physician, PM and local medical affairs Lead, and also global clinical lead, global patient safety physician and GMAL.

The SRC meeting will be held after the first 20 patients with PS2 have either completed the combination of durvalumab + chemotherapy (maximum of 6 cycles) or have discontinued treatment with durvalumab due to an AE or disease progression, whichever occurs first.

After review of the data in patients with PS2, and patients with PS0-1, the SRC will make a recommendation on whether the study should continue recruitment of patients with PS2 as planned, or hold recruitment of this patient population, or amend the study design. In the event that the SRC recommends a change to the study, this will be communicated to all sites.

There will be no formal interim analysis in this study.

The primary analysis of the study will be conducted 6 months after LSI, at which time secondary endpoints will also be assessed (maturity for PFS is approximately 60%). Additionally, final analysis will be performed at the end of the study when all patients have completed follow-up for safety or sufficient maturity for the secondary efficacy objectives has been reached.

2 INTRODUCTION

2.1 Background and rationale for conducting this study

2.1.1 Small cell lung cancer (SCLC)

Lung cancer has been the most common cancer in the world for several decades, with an estimated 1.8 million new cases in 2012 (12.9% of all new cancers), and was also the most common cause of death from cancer in 2012, with 1.59 million deaths (19.4% of the total cancer deaths; GLOBOCAN 2012).

Small-cell lung cancer (SCLC) represents approximately 13% of all newly diagnosed lung cancers (Puglisi et al 2010). SCLC is perhaps the most aggressive form of the disease, distinguishable from non-small-cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, and early dissemination. It is strongly associated with tobacco smoking and is also associated with an extremely high mutation rate. Inactivation of TP53 and RB1 occurs frequently, and in a recent study in which sequencing of SCLC tumors was carried out, recurrent mutations were identified in the CREBBP, EP300, and MLL genes that encode histone modifiers (Peifer et al 2012). Furthermore, mutations in PTEN, SLIT2, and EPHA7(as well as focal amplifications of the FGFR1 tyrosine kinase gene) were observed.

A 2-stage system dividing patients into limited and extensive disease was developed in 1973 by the United States (US) Veteran's Administration Lung Cancer Study Group. Limited disease was defined as tumor tissue that could be encompassed in a single radiation port, and extensive-stage (ES) was defined as any tumor that extended beyond the boundaries of a single radiation port. At present, limited disease is identified in ~30% of patients, and ES is identified in ~70% of patients.

Four to six cycles of platinum based chemotherapy, etoposide in combination with either cisplatin or carboplatin, without maintenance therapy has been the standard care (SoC) for patients with ES SCLC for the past 25 years (Pignon et al 1992, Roth et al 1992), and are recommended by major worldwide oncology treatment guidelines, ie, ASCO, NCCN, ESMO. Despite high initial response rates of up to 70% (Rossi et al 2012), it is estimated that 80% of patients with limited stage and almost all patients with ES SCLC will relapse or experience disease progression (Clark and Ihde 1998). Therefore, the prognosis for patients with SCLC in general and particular ES SCLC is poor; the reported 2-year survival is only 5% and 5 years survival rate is less than 2% (Rossi et al 2012).

2.1.2 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. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Hirano et al 2005

Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

Horn et al 2018
L.Horn, A.S. Mansfield, A.Szczesna, L.Havel, M.Krzakowski, M.J.Hochmair, F.Huemer, G.Losonczy, M.L Johnson, M.Nishio, M.Reck, T.Mok, S.Lam, D.S Shames, J.Liu, B.Ding, A.Lopez-Chavez, F.Kabbinavar,W.Lin, A.Sandler. and S.V.Liu for the Impower 133 Study Group First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer NEJM 2018 Sept, 25.

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-7.

Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Paz-Ares 2019

Luis Paz-Ares, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage

small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. LANCET. 2019 Oct 4. pii: S0140-6736(19)32222-6

Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to a 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 antitumor 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 pre-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, Horn et al 2018

L.Horn, A.S. Mansfield, A.Szczesna, L.Havel, M.Krzakowski, M.J.Hochmair, F.Huemer, G.Losonczy, M.L Johnson, M.Nishio, M.Reck, T.Mok, S.Lam, D.S Shames, J.Liu, B.Ding, A.Lopez-Chavez, F.Kabbinavar,W.Lin, A.Sandler. and S.V.Liu for the Impower 133 Study Group First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer NEJM 2018 Sept, 25.
Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Topalian et al 2012

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.

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 (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

Nivolumab and pembrolizumab, 2 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 SCLC, as well as metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma.

2.1.3 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 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 anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 7.5 Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

2.1.4 Durvalumab in combination with chemotherapy

Nonclinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1) can have a positive effect on antitumor immunity. Patients with SCLC may be particularly susceptible to these immunotherapies given the high mutational burden of this disease (Salgia and Skarin 1998). The use of combination chemotherapy is a mainstay of oncology therapy. The goal of combination chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus reducing the risk of developing resistance. Current investigations are now adding immunotherapeutics to chemotherapeutics to broaden antitumor responses.

Checkpoint inhibitors have been tested in SCLC, either used alone or in combination with chemotherapy. The IMpower133 study was presented at the World Congress on Lung Cancer (Horn et al 2018). IMpower133 was a randomized placebo-controlled phase III study, comparing atezolizumab + etoposide/carboplatin (EC) with placebo + EC in first line treatment of ES-SCLC. The study demonstrated a statistically significant improvement in OS with the combination of atezolizumab + etoposide/carboplatin compared to placebo + EC. Meanwhile, the CASPIAN study which was presented at the World Congress on Lung Cancer (Paz-Ares et al 2019) demonstrated a statistically significant improvement in OS of durvalumab plus etoposide/platinum (EP) compared to etoposide/platinum (EP) in first-line SCLC as well. CASPIAN was a randomised, open-label, phase 3 trial, to assess durvalumab, with or without tremelimumab, in combination with etoposide plus either cisplatin or carboplatin (EP) in treatment-naive patients with ES-SCLC. CASPIAN met its primary endpoint of overall survival for durvalumab plus EP versus EP at the planned interim analysis, with a hazard ratio of 0·73 (95% CI 0·59–0·91; p=0·0047]); median overall survival was 13·0 months (95% CI 11·5–14·8) in the durvalumab plus EP group versus 10·3 months (9·3–11·2) in the EP group. Any-cause adverse events of grade 3 or 4 occurred in 163 (62%) of 265 treated patients in the durvalumab plus EP group and 166 (62%) of 266 in the EP group; adverse events leading to death occurred in 13 (5%) and 15 (6%) patients in the two groups, respectively. Immune-mediated adverse events (imAEs) were reported in 52 (20%) of 265 patients treated with durvalumab plus EP and seven (3%) of 266 patients treated with EP alone, Most of these events were grade 1 or 2; grade 3 or 4 imAEs occurred in 12 patients (5%) in the durvalumab plus EP group and one patient (<1%) in the EP group. Deaths due to imAEs occurred in one (<1%) patient in each group; causes of death were hepatotoxicity in

the durvalumab plus EP group and pneumonitis in the EP group. The most common imAEs were hypothyroid events (occurring in 24 [9%] patients in the durvalumab plus EP group and two [1%] patients in the EP group) and hyperthyroid events (occurring in 14 [5%] and none in the two groups, respectively), which were all grade 1 or 2 in severity.

2.1.5 Rationale for conducting this study

ES-SCLC is an aggressive malignancy and the prognosis remains poor despite favorable initial response to platinum-based chemotherapy, which has been the standard treatment for over 3 decades. Recently, immunotherapy targeting the programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) pathway has demonstrated clinical activity for patients with ES-SCLC, including as first-line treatment. While the CASPIAN study demonstrated improved OS with the addition of durvalumab to carboplatin or cisplatin plus etoposide (Paz-Ares 2019), there remains unmet needs for improved treatments in first line ES-SCLC in China, particularly more safety data for patients who would not have been included in CASPIAN study, including the ECOG PS=2 population and for those patients for whom flexible number of chemotherapy cycles is important in treatment decision making.

2.2 Benefit/risk assessment

The following sections include summaries of the potential benefits and risks associated with durvalumab prior to the overall benefit-risk assessment. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of durvalumab may be found in the Investigator's Brochure.

2.2.1 Potential Benefits

2.2.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab monotherapy are based on the first-in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Overall, as of 7 May 2015, 456 of 694 patients treated with [redacted]

2.2.1.2 Durvalumab + chemotherapy

Studies evaluating agents targeting PD-L1 or CTLA-4 in combination with chemotherapy have yielded encouraging results.

The Phase III CASPIAN study demonstrated a statistically significant improvement in OS for durvalumab plus etoposide/platinum (EP) compared to EP alone as first-line treatment for ES-SCLC at a pre-planned interim analysis with a hazard ratio of 0·73 (95% CI 0·59–0·91; p=0·0047]). The median overall survival was 13·0 months (95% CI 11·5–14·8) in the durvalumab plus EP group versus 10·3 months (95% CI 9·3–11·2) in the EP alone group. The OS improvement with durvalumab plus EP was demonstrated across all pre-specified

subgroups. The secondary endpoint of progression free survival (PFS) was also improved with durvalumab plus EP versus EP (PFS HR: 0.78 [95% CI, 0.645–0.936]; median PFS, 5.1 vs. 5.4 months); the 12-month PFS rate was 17.5% vs. 4.7%, respectively. Durvalumab plus EP showed a 10% improvement in confirmed objective response rate (ORR) compared to EP; 67.9% vs. 57.6%, respectively. The treatment effects of durvalumab + EP were sustained over time compared to EP alone, as supported by the estimates of the 18 month OS rate, as well as the 12-month OS, PFS, and Duration of Response rates: 53.7% vs 39.8% of patients were alive at 12 months; an estimated 33.9% vs 24.7% of patients were alive at 18 months; and the 12-month PFS rate was 17.5% vs 4.7%, across the two groups, respectively.

2.2.2 Overall Risks

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

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

2.2.2.1 Durvalumab

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

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

In monotherapy clinical studies, AEs at an incidence of $\geqslant$ 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 (see Section 7.9.1).

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

2.2.2.2 Durvalumab + chemotherapy

The safety and tolerability of the combination of durvalumab plus chemotherapy was evaluated in two studies evaluating different chemotherapy regimens in patients with solid tumors: AZ study D419SC00001 and CCTG study NCT02537418. In general, the combination of durvalumab plus tremelimumab with chemotherapy appeared tolerable and manageable. On all dose levels, dose delays of durvalumab were mostly for administrative reasons/patient request and neutropenia related to chemotherapy.

In the randomized phase III CASPIAN study, durvalumab + EP was tolerable and manageable as first line treatment for ES-SCLC. The safety profile was consistent with the known profile of all the agents and no new safety signals were identified. In summary, any-cause adverse events of any grade were reported in 98.1% vs 97.0% of patients in the durvalumab +EP and EP alone groups, respectively. Rates of grade 3 or 4 occurred in 163 (62%) of 265 treated patients in the durvalumab plus EP group and 166 (62%) of 266 in the EP group; serious adverse events (SAEs) occurred in 30.9% of patients treated in the durvalumab plus EP group and 36.1% of patients treated in the EP group; adverse events leading to death occurred in 13 (5%) and 15 (6%) patients. Adverse events of any cause leading to discontinuation of study treatment occurred in 9.4% of the patients treated in both the durvalumab + EP and the EP alone groups. Immune-mediated adverse events (imAEs) were reported in 52 (20%) of 265 patients treated with durvalumab plus EP and seven (3%) of 266 patients treated with EP, Most of these events were grade 1 or 2 and were endocrine related; grade 3 or 4 imAEs occurred in 12 patients (5%) in the durvalumab plus EP group and one patient (<1%) in the EP group.

External clinical data also supports these findings. In the randomized Phase III study IMpower133 demonstrated that the safety profile of atezolizumab plus EC was consistent with the previously reported safety profile of the individual agents, with no new findings observed.

2.2.3 Overall benefit-risk assessment

There remains a significant unmet medical need for additional treatment options for patients with ES-SCLC. Four or six cycles of platinum-based chemotherapy has been considered the standard treatment regimens for the last several decades; however, OS remains poor with a 2-year survival rate of 5% despite favorable initial responses. The vast majority of ES-SCLC patients will relapse with a median time to progression of 4 to 6 months and a median OS of 7 to 11 months. The poor prognosis reflects the limited treatment options available, highlighting the need for the development of newer therapeutic options.

Recently, immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) pathway have demonstrated clinical activity across

multiple lines of therapy for patients with ES-SCLC.

In the Phase III CASPIAN study, durvalumab + EP demonstrated a statistically significant and clinically meaningful improvement in OS versus EP alone, reducing the risk of death by 27% for this challenging-to-treat disease. Importantly, these clinical benefits were observed in the context of a clinically relevant control arm that permitted up to 6 cycles of EP (compared with 4 cycles in the durvalumab + EP arm) and PCI at the investigator's discretion. Median OS was 13.0 versus 10.3 months for durvalumab plus EP versus EP alone and the OS benefit was observed across all clinically relevant patient subgroups. Consistent with the results for OS, PFS was also improved for durvalumab plus EP versus EP, as was confirmed ORR, with an incremental improvement of 10.3% between arms (67.9% vs. 57.6%). OS benefit was durable for durvalumab plus EP compared with EP, as evidenced by the tail of the Kaplan-Meier curve; in the durvalumab plus EP arm, an estimated 53.7% of patients were alive at 12 months and 33.9% of patients were alive at 18 months, compared to an estimated 39.8% and 24.7% of patients on the EP alone arm, respectively, at these landmarks. Sustained clinical benefit was also observed across PFS and tumor response with durvalumab plus EP versus EP, with 12-month PFS rates of 17.5% versus 4.7%, and 22.7% versus 6.3% of patients remaining in response at 12 months, respectively. These gains in long term clinical benefit are meaningful to patients with this recalcitrant disease.

[redacted]

3 OBJECTIVES AND ENDPOINTS

All objectives will be evaluated for all patients, unless otherwise indicated.

Primary objective:	Endpoint/variable:
To assess the safety and tolerability of durvalumab + EP in patients with performance status 0-2	Incidence of Grade ≥3 AEs Incidence of imAEs

AE Adverse event; EP Etoposide and platinum-based chemotherapy; imAE Immune-mediated adverse event.

Secondary objective:	Endpoint/variable:
To assess the efficacy of durvalumab + EP in patients with performance status 0-2	PFS, APF12, ORR, DoR using site Investigator assessment and OS, OS12
To further assess the safety and tolerability profile of durvalumab + EP	Incidence of AEs, SAEs, AESIs, AE resulting in treatment discontinuation

AESIs adverse event of special interest; DoR Duration of Response; EP Etoposide and platinum-based chemotherapy; ORR Objective response rate; OS Overall survival; OS12 Overall survival at 12 months after first dose of study treatment; PFS Progression free survival; APF12 Proportion of patients alive and progression free at 12 months after first dose of study treatment.

4 STUDY POPULATION

Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study at the screening visits. Under no circumstances will there be exceptions to this rule.

4.1 Inclusion criteria

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

1. Male or female ≥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 screening evaluations.
3. Histologically or cytologically documented extensive stage SCLC (stage IV [T any, N any, M1 a/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).
   - Brain metastases; must be asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment. Patients with suspected brain metastases at screening should have a CT/MRI of the brain prior to study entry.
4. 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.
5. Life expectancy ≥12 weeks at Day 1.
6. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 at enrollment.

- Note: Patients with PS2 will be limited to a maximum of 20% of the total study population; once this limit is met, additional enrolled patients must have PS 0-1.

7. Body weight >30 kg.
8. 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 computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.
9. Baseline CT/MRI results of the chest and abdomen (including liver and adrenal glands) within 28 days prior to the treatment initiation.
10. No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.
11. Adequate organ and marrow function as defined below (test can be repeated once if necessary):
    - Hemoglobin ≥9.0 g/dL.
    - Absolute neutrophil count ≥1.5 × 10^9/L (use of granulocyte colony-stimulating factor is not permitted within 7 days before testing).
    - Platelet count ≥100 × 10^9/L.
    - Serum bilirubin ≤1.5 × the upper limit of normal (ULN).
    - In patients without hepatic metastasis: ALT and AST ≤2.5 × ULN.
    - In patients with hepatic metastases, ALT and AST ≤5 × ULN.
    - Measured or calculated creatinine clearance: >60mL/min for patients planned to be treated with cisplatin and >40mL/min for patients planned to be treated with carboplatin
12. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause.

The following age-specific requirements apply:

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

4.2 Exclusion criteria

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

1. Previous IP assignment in the present study.

2. Medical contraindication to etoposide-platinum (carboplatin or cisplatin)-based

chemotherapy.

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

4. 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

5. Any condition that, in the opinion of the treating physician, would interfere with evaluation of the study drug or interpretation of patient safety.

6. Planned consolidation chest radiation therapy. Radiation therapy outside of the chest for palliative care (ie, bone metastasis) is allowed but must be completed before first dose of the study medication.

7. 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.
8. History of allogeneic organ transplantation.

9. Has a paraneoplastic syndrome (PNS) of autoimmune nature, requiring systemic treatment (systemic steroids or immunosuppressive agents) or has a clinical symptomatology suggesting worsening of PNS.

10. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis with the exception of diverticulosis, systemic lupus erythematosus, sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, and uveitis, etc]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia
- Patients with hypothyroidism (eg, following Hashimoto syndrome) and stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician
- Patients with celiac disease controlled by diet alone

11. 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.

12. History of active primary immunodeficiency.

13. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local

practice), hepatitis B (known positive HBV surface antigen [HbsAg] result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HbsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

14. 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). Premedication with steroids for chemotherapy is acceptable.

15. Receipt of live, attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

16. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from Screening to 90 days after the last dose of durvalumab.

For procedures for withdrawal of incorrectly enrolled patients, see Section 4.4.

4.3 Patient enrolment

At Screening (Days -28 to -1), the investigator(s) or suitably trained delegate(s) will perform the following:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed.
2. Determine patient eligibility. See Section 4.1 and Section 4.2.
3. Choose platinum agent that the patient would receive in cycle 1 (based on the most appropriate option for the patient).

The above does not list the exact sequence of study related procedures but provides the steps that should be taken during the screening period prior to baseline of the patient.

Patients must not be treated unless all eligibility criteria have been met.

Patients should begin treatment with durvalumab on Day 1 of Cycle 1 of EP.

4.4 Procedures for handling incorrectly enrolled

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but found to not meet all the eligibility criteria 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 incorrectly started on treatment, the investigator should inform the AstraZeneca 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.

4.5 Restrictions

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

1. Female patient of childbearing potential
    - Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 1) from the time of Screening and must agree to continue using such precautions for 90 days after the last dose of durvalumab. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.
2. Male patients with a female partner of childbearing potential
    - Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from Screening through 90 days after receipt of the final dose of durvalumab. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
    - 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 (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

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

chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as those that result in a low failure rate (ie, 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 (eg, 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).

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

Barrier/intrauterine methods	Hormonal methods
Copper T intrauterine device Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	Etonogestrel implants: eg, Implanon or Norplan Intravaginal device: eg, ethinylestradiol and etonogestrel Medroxyprogesterone injection: eg, Depo-Provera Normal and low-dose combined oral contraceptive pill Norelgestromin/ethinylestradiol transdermal system Cerazette (desogestrel)

a This is also considered a hormonal method.

3. Patients should not donate blood or blood components while Participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.
4. Restrictions relating to concomitant medications are described in Section 8.7.

4.6 Discontinuation of study treatment

An individual patient will not receive any further IP (durvalumab + EP or durvalumab monotherapy) 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 4.7.2).
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- An AE that meets criteria for discontinuation of durvalumab as defined in the Dosing Modification and Toxicity Management Guidelines (see section 7.9 and Annex to Protocol).
- Evidence of a new paraneoplastic syndrome(s) or worsening of an existing paraneoplastic

syndrome(s).
- Pregnancy or intent to become pregnant
- Noncompliance with the study protocol that, in the opinion of the investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including another investigational agent.
- Clinical progression or confirmed radiological progression per Investigator assessment (refer to Appendix C) and Investigator determination that the patient is no longer benefiting from treatment with IP.
- EP treatment should be discontinued after a maximum of 6 cycles
- EP treatment ⩽ 2 cycles
- Durvalumab treatment delayed > 12 weeks

[redacted]

4.6.1 Procedures for discontinuation of patient from IP

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 AEs. If possible, they will be seen and assessed by an investigator(s). AEs will be followed up (see Section 7).

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment.

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

4.7 Criteria for withdrawal

4.7.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not enter treatment. This reason for study withdrawal is only valid for screen failures (ie, not enrolled patients).

4.7.2 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 treatment in the study will not receive further IP, 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.

4.7.2.1 Survival status for patients who withdrew consent and were lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. 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.

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

- Lost to follow-up: site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status.
- In the 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 resources where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

5 STUDY PLAN AND TIMING OF PROCEDURES

This study has been subject to an internal review according to AstraZeneca standard procedures.

The latest version of the IB and any subsequent updates will be supplied to the investigator. Investigators need to become familiar with the content of the IB and appendices associated with this protocol.

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.
- For subsequent cycles the time between 2 consecutive doses cannot be less than 21 days, based on the half-lives of durvalumab. If there is a dosing delay while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.

Table 2 below outlines data collection measures that are considered for this study.

Table 2 Schedule of assessments

Visit	**Screening**	**Treatment period**			**Safety follow-up visit**	**Survival follow-up phone calls/emails**
		Baseline (Day1, Cycle 1)	**During Chemotherapy** 1 cycle = 21 days	**Post-Chemotherapy** 1 cycle = 28 days		
window	**Day-28 to Day-1**	**0**	**±3 days**	**±3 days**	**±7 days**	**±14 days**
Week	**Weeks-4 to Week-1**	**Week 0**	[redacted]	[redacted]	**90 days after last dose**	**Every 3 months**
Written informed consent[a]	X					
Inclusion/exclusion criteria	X					
Demographics, including baseline characteristics	X					
Medical history, including cancer treatment history	X					
ECG recording[b]	X	As clinically indicated				
Physical examination, weight, and vital signs	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	
Laboratory Assessments						
Clinical chemistry[c]	X	X[d]	X	X	X	
Hematology[c]	X	X[d]	X	X	X	
TSH, (reflex free T3 or free T4[f])	X	X[e]	X	X	X	

Visit	**Screening**	**Treatment period**			**Safety follow-up visit**	**Survival follow-up phone calls/emails**
		Baseline (Day1, Cycle 1)	**During Chemotherapy** 1 cycle = 21 days	**Post-Chemotherapy** 1 cycle = 28 days		
window	**Day-28 to Day-1**	**0**	**±3 days**	**±3 days**	**±7 days**	**±14 days**
Week	**Weeks-4 to Week-1**	**Week 0**	[redacted]	[redacted]	**90 days after last dose**	**Every 3 months**
Hepatitis B, C, HIV virology	X					
Pregnancy test[g]	X	X	X	X	X	
Urinalysis	X	As clinically indicated				
Monitoring						
AE	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	
IP Administration						
Durvalumab [h]		X	X	X		
Etoposide [i]		X	X [k]			
Carboplatin or cisplatin [i,j]		X	X [k]			
Tumor assessment per Investigator - report (according to RECIST1.1)[l]	X	On study tumor assessments should occur at Week 6±2 weeks, at Week 12±2 weeks then every 8±2 weeks[m] until PD				
Subsequent anticancer therapy					X	X
Survival status					X	X

a. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with

consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of first dose.

b. Any clinically significant abnormalities detected require triplicate ECG results.
c. Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.
d. 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.
e. If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
f. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
g. Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 3 weeks during chemotherapy and every 4 weeks post-chemotherapy. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.
h. Results for liver function tests, electrolytes, full blood count, and creatinine must be available before commencing an infusion (samples taken within 3 days prior to infusion) and reviewed by the treating physician or Investigator prior to dosing.
i. Durvalumab will be administered first, followed by the etoposide + cisplatin/carboplatin regimen.
j. If cisplatin, infuse over 1 to 2 hours. If carboplatin, infuse over 0.5 to 1 hour.
k. Chemotherapy regimen (etoposide plus either cisplatin or carboplatin) to be administered Q3W for 4 to 6 cycles, per investigator clinical decision.
l. See Section 6.1 and Appendix C for additional details relevant to image acquisition, RECIST 1.1 assessments, and evaluation of scans after RECIST 1.1-defined progression.
m. Patients will have scans done Q6W for the first 12 weeks, and then Q8W thereafter or per institutional standard at investigator discretion.

5.1 Screening/Enrollment period

All screening and enrollment procedures will be performed according to the assessment schedules in Table 2. Demographic data and other characteristics will be recorded including date of birth, gender and smoking history, etc, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. If laboratory or imaging assessments were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient.

Screening and baseline evaluations may be performed over more than 1 visit if required.

5.2 Treatment period

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

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.

5.3 Follow-up period

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up.

Patients who permanently discontinue drug for reasons other than objective disease

progression should continue to have tumor assessment until disease progression as per investigator assessment.

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

6 STUDY ASSESSMENTS

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.

6.1 Efficacy assessments

This study will evaluate the efficacy of durvalumab + EP as secondary endpoints, in terms of OS, as well as PFS, APF12, ORR, and DoR, which will be derived from site Investigator assessments per RECIST1.1.

Tumor assessments should 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. 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 SoA, Table 2). Treatment continues until clinical progression/deterioration or confirmed radiological progression (refer to Section 8.2.1), and scanning/tumor assessments should continue throughout treatment until RECIST 1.1-defined radiological progression plus an additional follow-up scan (if clinically feasible).

The RECIST 1.1 guidelines (Appendix C) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify Target Lesions (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, SD, PD, or Not Evaluable [NE]).

The date, procedure, and overall response should be documented at each follow-up visit time-point as well as if the patient is taking benefit from the study medication. In case of disease progression, the physician will assess, date, and document the progression and methods (eg CT scan) used as per standard definitions and routine institutional standard of care.

6.2 Survival assessments

The survival status of the patient will be collected during the study. After discontinuation of study treatment, patients will continue to be followed for survival via phone calls or email every 3 months to study end. The survival status (including cause of death) and the date of death or last follow-up date will be collected.

6.3 Safety assessments

6.3.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated Clinical laboratory safety tests, will be performed in a licensed clinical laboratory according to local standard procedures. 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 and according to standard medical practice. The date, time of collection, and results (values, units, and reference ranges) will be recorded. The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 7.3.6.

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies and HIV antibodies. T-spot TB test will be performed when determined to be essential by investigator.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Clinically significant (as assessed by the Investigator) laboratory abnormalities will be recorded as AEs. Laboratory results relevant to / associated with imAE will be recorded. will be

The laboratory variables to be measured are presented in Table 3 (clinical chemistry), Table 4 (hematology), and Table 5 (urinalysis).

Table 3 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]

Bicarbonate[c]	Total protein
Calcium	TSH[e]
Chloride[c]	T3 free[f] (reflex only)
Creatinine[d]	T4 free[f] (reflex only)
Gamma glutamyltransferase[c]	Urea or blood urea nitrogen, depending on local practice
Glucose	
Lactate dehydrogenase	

a Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
b It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.
c Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, magnesium, testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.
d Creatinine clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).
e If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
f Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid-stimulating hormone.

Table 4 Hematology

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Hemoglobin	Platelet count
Total white cell count	

a Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by Data Management if entered as percentage. Total white cell count therefore has to be provided.

Table 5 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at baseline (screening) and then as clinically indicated.
Note: Microscopy is preferred to investigate white blood cells, with use of high power field for red and white blood cells; dipstick can be used as well.

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix B 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.

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 7.3.6.

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

6.3.2 Physical examinations

At screening and each visit during the treatment period, a complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Physical examination information will only be reported in the CRF if abnormalities are reported as AEs.

6.3.3 Vital signs

Vital signs will be monitored at screening and at every visit during the study. During durvalumab infusions, vital signs should be monitored as per institutional care recommendations for the administration of monoclonal antibodies. Vital signs will be reported if abnormalities are reported as AEs.

6.3.4 Electrocardiograms

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

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

6.3.5 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see the SoAs) 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.

6.3.6 Other safety assessments

Safety findings supporting the monitoring and evaluation of imAEs, including radiographic or pathologic findings, or pulmonary function tests (in case of pneumonitis or ILD), should be reported.

7 SAFETY REPORTING AND MEDICAL MANAGEMENT

7.1 Definition of adverse events

An AE is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg,

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

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

7.2 Definitions of serious adverse event

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

- results in death
- is immediately life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/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

All SAEs (ie, those occurring after the AE and SAE collection period) considered to be reasonably related to the study treatments or to the research must be notified to the sponsor with no time limit.

7.3 Collection of adverse events

7.3.1 Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period up to 90 days after the last dose of durvalumab treatment. 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 SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix A. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

7.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

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

7.3.3 Adverse event data collection

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
- 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)
- Causality assessment in relation to other medication, as explained in Section 7.3.4
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 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 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 7.2. 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 7.2. 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 7.2.

7.3.4 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."

7.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to questions from the study site staff, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.3.6 Adverse events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

7.3.7 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 ULN together with total bilirubin ≥2 ULN may need to be reported as SAEs. Please refer to Appendix B for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

7.3.8 Disease-under-study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of extensive-stage small cell lung cancer. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

7.3.9 Disease progression

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

7.3.10 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.

7.3.11 Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. 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. 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 Patient 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.

7.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to durvalumab, or to the study procedure(s).

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

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

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

The reference documents for definition of expectedness are the IBs for durvalumab, as applicable to the tumor specific Module.

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.

7.5 Adverse events of special interest

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

AESIs for 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 aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

Other inflammatory responses that are rare/less frequent with a potential immune-mediated 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 etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 7.9.1 and Annex to the Protocol). 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.

7.6 Overdose

Durvalumab

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

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

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

Chemotherapy

Please refer to the local prescribing information for treatment of cases of overdose with etoposide, cisplatin or carboplatin.

7.7 Pregnancy

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

- Pregnancy discovered before the study patient has received any study drugs.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

7.7.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that durvalumab may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca study 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 provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 7.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.7.2 Paternal exposure

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

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of durvalumab 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.

7.8 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 eg, 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 eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient 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, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow up fatal/life-threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 7.8) and within 30 days for all other medication errors. The designated AstraZeneca representative will ensure a Medication Error Report Form is forwarded to site, completed and sent to AZ DES.

7.9 Management of investigational product-related toxicities

The following 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 where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections). This includes EP induced toxicity. In the event that toxicities are clearly attributed to chemotherapy, both EP and durvalumab should be delayed.
- In the absence of a clear alternative etiology, all events should be considered potentially immune related and the toxicity management guidelines detailed in the Annex to Protocol should be followed.
- In the event that durvalumab is temporarily discontinued or delayed as part of the toxicity management guidance, EP should still be administered as scheduled; every effort should be made to ensure patients receive at least 4 cycles of EP in the study, if conditions allow.

All toxicities will be graded according to NCI CTCAE, Version 5.0.

7.9.1 Specific toxicity management and dose modification information - Durvalumab

Comprehensive toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitor durvalumab [Medi4736] (PD-L1 inhibitor). These guidelines are applicable when durvalumab is administered concurrently or sequentially with other anti-cancer drugs (i.e. antineoplastic chemotherapy, targeted agents), 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 dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs 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” is provided to the investigative site as an Annex document 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 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 4.6 of this protocol and the Dosing Modification and Toxicity Management Guidelines). 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.

7.9.2 Chemotherapy

Chemotherapies are associated with a number of unwanted effects. EP-related toxicity management, dose adjustment, including dose delays and reductions should be performed as indicated in the local prescribing information for the relevant agent. In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point on study (assuming eligibility for the switched therapy is met).

EP is the SoC and is expected to cause hematologic non-immune-related AEs for which the non-immune-related Toxicity Management Guidelines should not be applied. Sites should utilize dose delays, dose modifications, G-CSF or component transfusions (eg, platelet transfusions) as necessary per local standards to maintain the dose and schedule of EP treatment to optimize tolerability for individual patients.

In the event that an AE can reasonably be attributed to EP, dose adjustment of EP should be attempted before modifying the administration of durvalumab.

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.

8 INVESTIGATIONAL PRODUCT AND OTHER STUDY TREATMENTS

8.1 Identity of investigational products

AstraZeneca will supply durvalumab (MEDI4736)and EP treatments (Table 6)

Table 6 List of investigational products for this study

Investigational product	Dosage form and strength

Durvalumab	500 mg vial solution for infusion after dilution, 50 mg/mL, IV
Etoposide	IV (as sourced locally)
Carboplatin	IV (as sourced locally)
Cisplatin	IV (as sourced locally)

8.1.1 Order of Administration

Patients will receive durvalumab [redacted] via IV infusion over 60 minutes on Day 1 of each cycle.

We recommend a 60-minute observation period after durvalumab is administered at least for cycle 1.

If no issues are seen after durvalumab is given during the first cycle, we recommend reducing the observation period after durvalumab administration to 30 minutes.

Durvalumab will then be followed by carboplatin or cisplatin as an IV infusion over 60 minutes on Day 1 of each cycle, for a maximum of 6 cycles, followed by etoposide sequentially administered by a 60-minute IV infusion on Days 1, 2, and 3 of each cycle, for a maximum of 6 cycles.

8.1.2 Durvalumab (MEDI4736)

[redacted]

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

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

[redacted]

[redacted]

If weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be a administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) [redacted] and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Standard infusion time 1 hour. In the event that 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 and document if the line was not flushed.

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.

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

8.1.3 EP

EP will be supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the Investigating site.

8.2 Dose and treatment regimens

During Chemotherapy

Agent	Dose	Route	Duration	Schedule
[redacted]	[redacted]	IV	60 mins	4 to 6 doses with EP Q3W
EP	[redacted]	IV	Per local practice	4 to 6 doses Q3W

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q3W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab [redacted].
EP Etoposide and platinum-based chemotherapy; IV Intravenous; Q3W Every 3 weeks.

Post-Chemotherapy:

Agent	Dose	Route	Duration	Schedule
[redacted]	[redacted]	[redacted]	60 mins	Q4W to PD*

[redacted]

8.2.1 Duration of treatment and criteria for treatment through progression

All treatment will be administered beginning on Day 1.

Treatment with SoC chemotherapy (EP) will be limited to 6 cycles on a Q3W schedule, at the investigators' discretion.

Durvalumab will be administered beginning on Day 1 until PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and patient as long as they are deemed to be receiving clinical benefit. A follow-up scan is to be collected after the initial RECIST 1.1-defined PD, 4-8 weeks after the prior assessment of PD.

Patients who continue to receive IP at the discretion of the Investigator can receive treatment until they are no longer deemed to be receiving clinical benefit or end of the study, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Image acquisitions and tumor assessments should continue on their regular imaging schedule for the duration of treatment.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, 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 treatment would not further benefit the patient.

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.

Following confirmed disease progression, standard chemotherapy can be offered by the investigator per local practice.

8.3 Labeling

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

Labels will be provided as a single panel label.

8.4 Storage

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

The package inserts for etoposide/carboplatin/cisplatin specifies the appropriate storage for these agents.

8.5 Compliance

The administration of each study drug should be recorded in the appropriate sections of the eCRF.

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

8.6 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.
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.

8.7 Concomitant medications 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 (final study visit), including the Follow-up perio[redacted] 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 Table 7 and

Table 8. Refer also to the Dosing Modification and Toxicity Management Guidelines (see section 7.9.1 and Annex to Protocol).

Table 7 Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
Investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the immuno-oncology infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs. • Short-term premedication for patients receiving combination agents SoC, in which 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 intra-nasal 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 (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).

Prohibited medication/class of drug:	Usage:
EGFR TKIs	[redacted] 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

AE Adverse event; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; EGFR Epidermal growth factor receptor; IP Investigational product; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1; SoC Standard of care; TKI Tyrosine kinase inhibitor.

Table 8 Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, G-CSF and other hematopoietic factors, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

8.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the physician and recorded appropriately.

8.7.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either preclinically 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.

8.8 Rescue medication

As a result of imAEs that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). Rescue medications will be sourced per local practice.

9 STATISTICAL ANALYSES

9.1 Statistical considerations

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

A comprehensive statistical analysis plan (SAP) will be prepared and finalized before first patient in (FPI) 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 assess the safety and tolerability of Durvalumab + EP in patients with performance status 0-2.

9.2 Sample size determination

This is a safety study and no formal sample size calculation will be done. However, assuming AE of CTCAE grade ≥3 with an incidence of 60%, approximately 300 patients are needed to achieve the estimation precision no wider than 5.7% based on exact method (Clopper-Pearson). In addition, assuming the imAE with an incidence of 20%, the estimation precision will be no wider than 4.7% using the same method. An illustration of the precision around the varying incidences of AE for the patients enrolled is provided in Table 9.

Table 9 Precision around varying incidence of AE

Sample Size	Precision achieved with different assumed incidence of AE				
	20%	40%	50%	60%	70%
200	5.8%	7.0%	7.1%	7.0%	6.6%
300	4.7%	5.7%	5.8%	5.7%	5.3%
500	3.6%	4.4%	4.5%	4.4%	4.1%

9.3 Definitions of analysis sets

9.3.1 Safety analysis set (SAS)

The safety analysis set will include all subjects who received at least one dose of study treatment.

9.3.2 Efficacy analysis set

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

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs, ECG and exposure. These will be collected for all patients.

Adverse events

Adverse events will be summarized as follows in terms of both Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade:

AE: Number and proportion of patients with AEs in total and by causality and severity

AE with Grade ≥3: Number and proportion of patients with Grade ≥3 AEs

SAE: Number and proportion of patients with SAEs in total and by causality and severity

AEs leading to death: Number and proportion of patients with AEs leading to death

AEs leading to treatment discontinuation: Number and proportion of patients with AEs leading to treatment discontinuation

AESIs: An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. Please refer to Section 7.5. In order to further characterize safety objectives related to AESIs, outcome measures will be assessed, which may include (and are not necessarily limited to) the following:

(a) Number and proportion of patients with AESIs, by pre-defined type (or newly defined by this study) in total and by seriousness, severity and causality, including immune-relatedness;

(b) Number and proportion of patients who received steroids, immunosuppressants and/or hormone replacement therapy to manage AESIs;

(c) Time from start of durvalumab (MEDI4736) to the onset of an AESI pre-defined type, all

interventions of AESIs by type of intervention (including intervention with steroids, immunosuppressants and/or hormone replacement therapy), and time from onset of an AESI type to resolution;

(d) Duration of the intervention with steroids, immunosuppressants and/or hormone replacement therapy until the resolution of AESI;

(e) Laboratory findings, vital signs and other safety parameters associated with AESIs will be summarized as part of the AESI outcome measures.

imAEs: The imAEs will be assessed as a subset of AESIs. Please refer to Section 7.5.

Any AE occurring before treatment with study drug 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 durvalumab will be included in the AE summaries.

9.4.2 Calculation or derivation of efficacy variables

Investigator assessments

At each visit, patients will be programmatically assigned a response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments (by investigator assessment according to RECIST v1.1 criteria). If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is any evidence of progression in which case the response will be assigned as PD. Please refer to Appendix C for the definitions of CR, PR, SD, and PD. The investigator assessments will be used in the calculation of PFS, APF12, ORR and DoR.

Progression free survival

Progression-free survival is defined as the time from first dose of study treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment of investigator. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at the day of first dose unless they die within 2 visits of baseline.
The PFS time will always be derived based on scan/assessment dates not visit dates.

The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Proportion of patients alive and progression free at 12 months

The APF12 will be defined as the Kaplan-Meier estimate of PFS (per investigator assessment according to RECIST v1.1 criteria) at 12 months.

Objective Response Rate

Objective Response Rate is defined as the number (%) of patients with measurable disease with at least 1 visit response of CR or PR. Data obtained up until progression or last evaluable assessment in the absence of progression will be included in the assessment of ORR. If any patients do not have measurable disease at baseline then the analysis of ORR will exclude these patients, so that the denominator is a subset of the SS who have measurable disease at baseline.
However, any CR or PR which occurred after a further anti-cancer therapy was received will not be included in the numerator for the ORR calculation.

Duration of Response

Duration of response is only calculated for patients who have a best overall tumor response of CR or PR before subsequent anti-cancer therapy. Duration of response will be defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

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

Overall survival

Overall survival is defined as the time from the date of first dose of study treatment 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.

Proportion of patients alive at 12 months

The OS12 will be defined as the Kaplan-Meier estimate of OS at 12 months.

9.5 Methods for statistical analyses

Analysis for this study will mostly be descriptive. Continuous variables will be summarised by the number of observations (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Two-sided 95% CIs will be provided as appropriate. Approximately, 300 patients will be enrolled to this study. All subjects who received at least 1 dose of study treatment will be included in the safety analysis set, which will be the primary analysis set for all analyses.

9.5.1 Analysis of the primary variables

One of the primary outcome measures for the study is the frequency and percentage of patients with AEs of CTCAE grade ≥3, and it will be summarized by System Organ Class and preferred term. The same summary table will be generated by maximum CTCAE grade and by relationship to the treatment. AEs of CTCAE grade ≥3 (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The Clopper-Pearson 95% CIs around the incidence rate will also be reported.

Similar analyses will be conducted for imAEs.

9.5.2 Analysis of the secondary variables

One of the secondary objectives is to assess the efficacy of first-line durvalumab + EP in terms of PFS, ORR, DoR and OS. PFS (by investigator assessment according to RECIST v1.1 criteria) is defined as the time from first dose of treatment until the date of objective PD or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. ORR is defined as the percentage of patients with a best response of CR (complete response) or PR (partial response) by investigator assessment according to RECIST v1.1 criteria. DoR will be defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. OS is defined as the time from first dose of treatment until death due to any cause. Time-to-event data (PFS, OS) will be summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% CIs, given the anticipated maturity of 60%. The Kaplan-Meier curves will be provided. The proportion of patients alive and progression free at 12 months (APF12), the proportion of patients alive at 12 months (OS12) will be summarized (using the Kaplan-Meier curve). ORR will be summarized descriptively, and the Clopper-Pearson 95% confidence intervals (CIs) will be provided. A median duration of response and associated 95% confidence interval will be calculated for responding patients.

Analyses similar to the primary endpoints will be conducted for overall AEs, SAEs, AESIs and AEs leading to discontinuation of study treatment. In addition, the number and percentage of patients with AEs will be presented by PT. Time to event endpoints will be analysed using Kaplan-Meier estimates of the median event time.

9.5.3 Subgroup analysis

Subgroup analysis of safety and efficacy will be conducted for the cohorts of patients with PS 0 to 1 and 2 at baseline. For time to event analysis, each subgroup must have at least 20 events per subgroup level in order for that subgroup level to be included in the subgroup analysis. Additional subgroup analyses may be conducted for safety and efficacy parameters based on the following and will be defined in the SAP as appropriate:

- Platinum received in Cycle 1 (cisplatin versus carboplatin)
- Sex (male versus female)
- Age (<65 versus ≥65 years of age)

- Smoking status (current versus former versus never smoker)
- Number of cycles of EP (≤4 versus > 4)
- Use of PCI (yes versus no)

Other baseline variables may also be assessed pending clinical justification. The purpose of the subgroup analyses is to assess the consistency of effect across expected prognostic and/or predictive factors. Forest plot(s) will be generated.

9.5.4 Interim analysis

There will be no formal interim analysis in this study.

As the safety of durvalumab + EP has not been previously established in ES-SCLC patients with PS2, a safety review committee (SRC) will be established to review the safety and tolerability data of the combination of Durvalumab+EP in this subset of patients at an early stage of enrolment. SRC will include AZ local study team member such as study physician, PV physician, PM and local medical affairs Lead, and also global clinical lead, global patient safety physician and GMAL.

The SRC will meet after the first 20 patients with PS2 have either had the opportunity to complete the combination of durvalumab + chemotherapy (maximum of 6 cycles) or have discontinued treatment with durvalumab due to an AE or disease progression, whichever occurs first.

After review of the data in patients with PS2, and patients with PS0-1, the SRC will make a recommendation on whether the study should continue recruitment of patients with PS2 as planned, or hold recruitment of this patient population, or amend the study design. In the event that the SRC recommends a change to the study, this will be communicated to all sites.

The primary analysis of the study will be conducted 6 months after LSI, at which time secondary endpoints will also be assessed (maturity for PFS is anticipated to be approximately 60%).

Additionally, final analysis will be performed at the end of the study when all patients have completed follow-up for safety or sufficient maturity for the secondary efficacy objectives has been reached.

10 STUDY MANAGEMENT BY ASTRAZENECA REPRESENTATIVE

10.1 Training of study site personnel

Before the first patient is enrolled in the study, an AstraZeneca representative or delegate 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.

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).

10.2 Monitoring of the study

During the study, an AstraZeneca representative or delegate 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 (eg, clinic charts).

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.

10.2.1 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of the 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.

10.2.2 Archiving of study documents

The investigator follows the principles outlined in the CSA.

10.3 Study timetable and end of study

After patients have discontinued from durvalumab treatment, other available treatment options will be at the discretion of the physician.

Enrolment will be closed as soon as the product receives China marketing authorization as first line treatment for ES-SCLC or total 300 sample size is achieved, whichever comes first. Treatment will continue to be provided to all patients who are already enrolled to the study and who are still deriving benefit, until disease progress or study end.

The end of the study is defined as "the last visit of the last patient undergoing the study". The study will be end when all patients have completed follow-up for safety or sufficient maturity for the secondary efficacy objectives has been reached, which will estimate to be end by Q4, 2022.

The study may be terminated at individual centers if the study procedures are not being performed

according to GCP.

11 ETHICAL AND REGULATORY REQUIREMENTS

11.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

11.2 Patient data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
AstraZeneca or its representative will not provide patient information to patients, any insurance company, any employer, their family members, general physician or to any other third party, unless required to do so by law.
Precautions are taken to preserve confidentiality and prevent data being linked to the identity of the patient. Also Regulatory authorities may require access to the relevant files.

11.3 Ethics and regulatory review

An Independent Review Board (IRB)/Ethics Committee (EC) must 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, as per local regulations. The opinion of the IRB/EC must be given in writing.

AstraZeneca or its representative must approve any modifications to the ICF that are needed to meet local requirements.

Before enrollment of any patient into the study, the final protocol, including the final version of the ICF, is to be approved by the national regulatory authority or a notification to the national regulatory authority is to be done, according to local regulations.

AstraZeneca or its representative will provide Regulatory Authorities, IRB/EC, and investigators with safety updates/reports according to local requirements.

Each investigator is responsible for providing the IRB/EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca or its representative will provide this information to the investigator so that he/she can meet these reporting requirements.

11.4 Informed consent

The investigator at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to

consider the information provided.
- Ensure each patient or legally acceptable representative provides signed and dated ICF before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the investigator's study file.
- Ensure 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 informed consent form that is approved by an IRB/EC.

11.5 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a protocol amendment and where required in a new version of the study protocol (Revised Study Protocol).

The amendment is to be approved by the relevant IRB/EC and if applicable, the national regulatory authority needs also to be notified or has to provide approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca or its representative will distribute any subsequent amendments and new versions of the protocol to each participating investigator. For distribution to IRB/EC, see Section 11.3.

If a protocol amendment requires a change to a site's ICF, AstraZeneca (or its representative) and the site's IRB/EC 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 IRB/EC.

11.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB/EC may perform audits or inspections at the study site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the study site.

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Appendix A Adverse event definitions and additional safety information

A 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

A 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 treatment to prevent one of the outcomes listed above.
- Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs if not the same as the primary tumour under investigation. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical bjudgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-

Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

- Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

A 3 Life threatening

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

A 4 Hospitalization

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

A 5 Important medical event or medical treatment

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

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

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

A 6 CTCAE grade

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix A2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix A2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix A2.

A 7 A guide to interpreting the causality question

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

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

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

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

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

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

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

A 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 participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error (eg, medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated, for example, wrong route or wrong site of administration

- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the fridge when it should be at room temperature)
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix B Actions required in cases of increases in liver biochemistry and evaluation of Hy's law

B 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in the Dosing Modification and Toxicity Management Guidelines.

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 product (IP).

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.

B 2 Definitions

Potential Hy's law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's law (HL)

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

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

B 3 Identification of potential Hy's law cases

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

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

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

- Determine whether the patient meets PHL criteria (see Appendix B2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

B 4 Follow-up

B 4.1 Potential Hy's law criteria not met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

B 4.2 Potential Hy's law criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 7.4 Safety Reporting)
- 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.

- 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.

B 5 Review and assessment of potential Hy's law cases

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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient 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 IP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

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

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

B 6 Actions required when potential Hy’s law criteria are met before and after starting study treatment

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

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the patients’ condition[#] compared with the last visit where PHL criteria were met.

- If there is no significant change, no action is required

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix A 5.

- *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.

B 7 Actions required for repeat episodes of potential Hy’s law

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

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

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

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease)

If **No**: Follow the process described in Appendix B4.1

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 Appendix B4.

*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.

Appendix C 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 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 organomegaly identified by physical examination that is not measurable by CT or MRI.
- Tumour lesions selected for screening biopsy
- Previously irradiated lesions[2]

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

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

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

Table 10 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 tumour 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 tumour 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

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

should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with 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 12 weeks, 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±2 weeks for 12 weeks (relative to the date of randomization) then every 8±2 weeks until confirmed objective disease progression.

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 11).

Table 11 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 12).

Table 12 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 13.

Table 13 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 and/or pre-existing new lesions at the confirmatory scan time-point compared with the prior time-point (Note: Pre-existing 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.

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.