Clinical Study Protocol	
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A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN)

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
001	CCI [redacted]		
002			
003			
004			
005			

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

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VERSION HISTORY

Version 6.0, CCI [redacted]
Updates per Durvalumab IB edition 15 and Tremelimumab IB edition 10. **Sections updated: 1.3.2.1, 1.3.2.2, 1.3.2.3** New CSP language on malignancies. **Section updated: 6.2** Updated AESI list for Durvalumab. **Section updated: 6.5** Updated language when applying Toxicity Management Guidelines as a standalone clinical document. **Sections updated: 1.3.2.1, 3.9, 5.2.7, 6.5, 6.9, 6.9.1, 7.7** Addition of language regarding long-term follow up and clarification of data collection post primary database lock. **Sections updated: 4.3, 5.1.2, 9.3, 9.4, added Table 12** **Appendix E [Dose Modification and Toxicity Management Guidelines]:** This section was removed to have Toxicity Management Guidelines as a standalone Annex.
Version 5.0, CCI [redacted]
Update of Multiple Testing Procedure (MTP). **Sections updated: Synopsis, 8.2, 8.5, 8.5.10 and Figure 6**
Version 4.0, CCI [redacted]
Update of primary and secondary objectives and the rationale, removal of BICR. **Sections updated: Synopsis, List of abbreviations and definitions of terms, Sections 1.1.5.1, 1.2.4, 1.3.1.3, 1.3.2.4, 2.1, 2.2, 4, 5.1, 5.1.1, 8.4.1.1, 8.4.1.3, 8.5.2.1, 8.5.2.2, Table 11, Figure 3, and Appendix F** Update of Multiple Testing Procedure (MTP) and interim analysis plan including maturity. Sections updated: **Synopsis, 8.1, 8.2, 8.3, 8.4.1.1,8.4.1.2, 8.4.1.3, 8.5, 8.5, 8.5.1.1, 8.5.2.1, 8.5.2.2, 8.5.2.3, 8.5.2.4, 8.5.10, 8.6, Figure 3 and Table 11** Clarification regarding follow up scan . **Sections updated: Figure 4, Figure 4 footnote b, Table 3 and Appendix F**

Clarification on PK non-compartmental analysis and patient reported outcomes. **Sections updated : 8.4.4.2 and 8.5.3.3** Minor administrative changes for clarification and to correct typographical errors
Version 3.0, CCI [redacted]
Update of primary and secondary objectives. **Sections updated: Synopsis, Sections 1.2.4, 2.1 and 2.2** Update of information regarding primary and secondary variables, MTP and alpha allocation, interim analysis, power, critical values of hazard ratio for PFS and OS analyses, projected number and percentage of PFS and OS events at interim/final analyses, projected alpha allocation at interim/final analyses and projected study duration. **Sections updated: Synopsis, Sections 8.1, 8.2, 8.5, 8.5.1.1, 8.5.1.2, 8.5.10, Figure 6 and Table 11** Clarification regarding time period for collection of adverse events. **Section updated: Table 3 footnote C.** Removal of the information that samples taken for paraneoplastic auto-antibody research will be used for retrospective TMB analysis. **Section updated: Section 5.5.1.** Addition of information regarding safety data to be collected following the final DCO of the study**. Section updated: Section 6.3.12.** Addition of language to allow long term survival follow up post analysis of OS. **Sections updated: Synopsis, Sections 5.1.2, 6.3.12, 9.3 and Table 3 footnote f.** Addition of information regarding the request for at least one subsequent scan after each initial progression event for all patients if possible**. Sections updated: Section 4, Table 2, Table 2 footnote f and Table 3** Removal of mainland China to allow patients dosed in CFDA approved sites in Taiwan to be included and correction to the definition of China Cohort. **Sections updated: Synopsis, list of abbreviations and definitions of terms Sections 1.4, 2.4, 8.2 and 8.6** Addition of information regarding the preparation of durvalumab and tremelimumab doses for administration with an IV bag. **Sections updated: Sections 7.1.2 and 7.1.3** Removal of the information regarding confirming responses**. Sections updated: Section 5.1**

Change to language regarding treatment through progression. **Sections affected : Synopsis and Section 7.2**

Removal the references to irRECIST. **Sections updated: list of abbreviations and definitions of terms, Sections 1.2.4, 5.1.1, 8.4.1.1, 8.4.1.2, 8.5.1.2 and Table 11**

Clarification regarding the collection of second progression and subsequent anticancer therapy. **Sections updated: Section 8.4.1.4 and Table 3**

Additional information regarding analysis of Patient-reported outcomes. **Sections updated: Sections 8.4.3 and 8.5.3.**

Minor administrative changes for clarification and to correct typographical errors

Version 2.0, CCI [redacted]

Changes to the protocol are summarized below:

Update to the Toxicity Management Guidelines, to be consistent with updates across the clinical programme and to the Investigator's Brochure. The main changes are to the General Guidance section, addition of specific guidance for myocarditis and myositis/polymyositis, and update to specific guidance for Endocrinopathy. **Sections updated: Sections 4, 6.9 and Appendix E.**

A 2-day window has been added to Cycle 1, Day 1 to allow the administration of study treatment to start up to 2 days after randomization, in order to allow sites sufficient time to prepare and label the study treatments. **Sections updated: Figure 4, Table 2, Sections 3.3 and 7.2.2).**

Updates to the descriptions of risks for durvalumab, tremelimumab, and the combination of durvalumab + tremelimumab, in line with updates across the clinical programme. **Sections updated: Sections 1.3.2, 1.3.2.1, 1.3.2.2, and 1.3.2.3.**

Clarification that the APF6, APF12 and OS18 endpoints are equivalent to PFS at 6 months, PFS at 12 months and OS at 18 months, respectively. **Sections updated: Synopsis, List of abbreviations, and Sections 1.2.4 and 2.2.**

Updates to the Adverse Events of Special Interest. **Section updated: Section 6.5.**

The 7-day window has been removed from the checks on survival status for those patients who have withdrawn consent or are lost to follow-up. **Section updated: Section 3.10.2.1.**

Addition of options to continue recruitment in mainland China, following achievement of the global recruitment target of 795 randomized patients and a further objective to evaluate consistency in efficacy and safety among SCLC patients in mainland China, as required by the China Food and Drug Administration. **Sections updated: Synopsis, Sections 1.4, 8.2, and 8.6.**

To include an exploratory objective to investigate the relationship between a patient's tumor mutational burden (TMB) and efficacy outcomes. **Sections updated: Table 2, Sections 2.4 and 5.5.1.** Updates and clarification of the description of guidelines for evaluation of objective tumor response using RECIST 1.1. **Sections updated: Section 5.1 and Appendix F.** Removal of the paraneoplastic auto-antibody research at selected sites; samples collected so far on study will be used for TMB analysis. These analyses have been removed due to sub-optimal sample collection at selected sites and limited sample stability. Any samples collected for this purpose (as per Version 1.1 of the CSP) will be used for retrospective TMB analysis, subject to receipt of re-consent. This will ensure utilization of all samples collected on study and will enrich the sample set for the TMB analysis, as it will provide baseline samples for some of the patients already randomized in CASPIAN. **Sections updated: Table 2, Table 3, Section 3.1 and Section 5.5.1.** Addition of text to describe how patients can continue to receive their assigned treatment after the final data cut-off (DCO). **Section updated: Synopsis, Section 7.2.2.** Minor administrative changes for clarification and to correct typographical errors.
Version 1.1, CCI [redacted]
Initial creation

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

PROTOCOL SYNOPSIS

A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN)

International Coordinating Investigator.

PPD

Study site(s) and number of patients planned

This study will randomize approximately 795 eligible patients to receive durvalumab + tremelimumab + etoposide and cisplatin or carboplatin (etoposide and platinum-based chemotherapy [EP]; Arm 1), durvalumab + EP (Arm 2), or EP alone (Arm 3) at sites worldwide. Once global enrollment achieves 795 randomized patients, recruitment will continue in China only. Up to 189 patients from China will be randomized into the study (see Section 8.6 for detail). The choice of platinum agent is at the Investigator's discretion, but must be in accordance with eligibility criteria.

Study design

This is a phase III, randomized, open-label, multicenter, global study to determine the efficacy and safety of combining durvalumab ± tremelimumab with EP followed by durvalumab ± tremelimumab maintenance therapy versus EP alone as first-line treatment in patients with extensive-disease small-cell lung cancer (SCLC).

This study is planned to randomize approximately 795 eligible patients at sites worldwide. Patients who fulfill all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1:1 ratio in a stratified manner according to the planned platinum-based therapy for Cycle 1 (cisplatin or carboplatin) to receive treatment with durvalumab + tremelimumab + EP (Arm 1), durvalumab + EP (Arm 2), or EP (Arm 3).

Durvalumab with or without tremelimumab will be concurrently administered with first-line chemotherapy (EP) in the experimental arms (Arm 1 and Arm 2) and will continue to be administered post-chemotherapy until confirmed progressive disease (PD). The control arm (Arm 3) can receive up to 6 cycles of EP and prophylactic cranial irradiation if clinically indicated, at the Investigators' discretion.

Tumor assessments will be performed at Screening as baseline with follow-up at Week 6 ±1 week from the date of randomization, at Week 12 ±1 week from the date of randomization, and then every 8 weeks ±1 week until confirmed objective disease progression.

Global recruitment will be completed once approximately 795 patients have been randomized. Once global enrollment is completed, recruitment will continue in China only. A total of up to 189 patients from China will be randomized (see Section 8.6 for detail).

Objectives

Primary objective:	**Outcome measures:**
To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and the efficacy of durvalumab + EP treatment compared with EP in terms of OS	OS

EP Etoposide and platinum-based chemotherapy; OS Overall survival.

Secondary objectives:	**Outcome measures:**
To further assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and the efficacy of durvalumab + EP compared with EP in terms of PFS, ORR, APF6 (PFS rate at 6 months), APF12 (PFS rate at 12 months), and OS18 (OS rate at 18 months)	PFS, ORR, APF6 and APF12 using site Investigator assessments according to RECIST 1.1 OS18
To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with durvalumab + EP in terms of PFS and OS	PFS using site Investigator assessments according to RECIST 1.1 OS
To assess the PK of both durvalumab and tremelimumab	Concentration of durvalumab and tremelimumab in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling)
To investigate the immunogenicity of durvalumab and durvalumab + tremelimumab	ADA (confirmatory results: positive or negative; titers [ADA neutralizing antibodies will also be assessed])

Secondary objectives:	Outcome measures:
To assess the effect of treatment on SCLC symptoms and health-related QoL using EORTC QLQ-C30 v3 and QLQ-LC13	EORTC QLQ-C30: symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Health-related QoL/functioning (physical function, role function, emotional function, cognitive function, social function, and global health status/QoL). EORTC QLQ-LC13: disease-related symptoms (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and other pain). Changes in WHO/ECOG performance status will also be assessed.

ADA Anti-drug antibody; AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomization (ie, PFS rate at 12 months); APF6 Proportion of patients alive and progression free at 6 months from randomization (ie, PFS rate at 6 months); ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EP Etoposide and platinum-based chemotherapy; OS Overall survival; OS18 Overall survival at 18 months after randomization; PFS Progression-free survival; PK Pharmacokinetic(s); QLQ C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; WHO World Health Organization.

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of durvalumab and durvalumab + tremelimumab in combination with EP treatment compared with EP	AEs; physical examinations; vital signs including blood pressure and pulse rate; and laboratory findings including clinical chemistry, hematology, and urinalysis

AE Adverse event; EP Etoposide and platinum-based chemotherapy.

A further objective, to fulfil China Food and Drug Administration (CFDA) requirements, is to evaluate the consistency in efficacy and safety among patients from China for benefit-risk assessment of durvalumab + tremelimumab in combination with EP treatment compared to EP and durvalumab + EP compared to EP.

Target patient population

Adult patients (aged ≥18 years) with histologically or cytologically documented extensive disease (American Joint Committee on Cancer Stage (7th edition) IV SCLC [T any, N any, M1 a/b]), or 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. Patients must have World Health Organization/Eastern Cooperative Oncology Group performance status of 0 or 1.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients in Arms 1 and 2 will continue therapy until disease progression, as per investigator assessment. Unless specific treatment discontinuation criteria are met, treatment can continue for up to 6 cycles for patients in Arm 3.

Patients who continue to receive benefit from their assigned treatment at the final data cut-off (DCO) and database lock may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database lock, it is recommended that the patients continue the scheduled site visits according to the limited schedule in section 9.3. and investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage adverse events (AEs) in accordance with the durvalumab toxicity management guidelines.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database lock, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits assessments per its protocol. Any patient who would be proposed to move to such study would be given a new informed consent form.

Progression during treatment

Patients in all arms with PD by RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment for as long as they are gaining clinical benefit. This also applies to EP; however, EP is restricted to a maximum of 4 cycles for patients in Arms 1 and 2 and a maximum of 6 cycles for patients in Arm 3.

Follow-up of patients post-discontinuation of study drug

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

Survival

All patients randomized in the study should be followed up for survival. Survival assessments may continue per protocol (every 2 months) post the primary analysis of OS unless instructed otherwise by AstraZeneca.

Investigational product, dosage, and mode of administration

- Durvalumab 1500 mg ± tremelimumab 75 mg will be administered via IV infusion, concurrently with chemotherapy starting on week 0 and continued post

chemotherapy. In Arm 1 up to 5 combination doses of durvalumab + tremelimumab will be administered; the detailed dose and schedule is illustrated in Figure 1

- N.B. If a patient's weight falls to 30 kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab and 1 mg/kg tremelimumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg plus tremelimumab 75 mg.

- EP: the dose of etoposide + carboplatin or cisplatin investigated will not exceed the product label dose for the given indication dose (etoposide [80 to 100 mg/m^2] via IV infusion with either carboplatin [area under the curve (AUC) 5-6] via IV infusion or cisplatin [75 to 80 mg/m^2] via IV infusion) starting on Week 0, for up to a maximum of 4 doses/cycles in Arms 1 and 2 and a maximum of 6 cycles in Arm 3.

Figure 1 Dosing Scheme

Treatment arms	During Chemotherapy Q3W				Post Chemotherapy Q4W		
	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Week 12	Week 16	Week 20 to PD
Arm 1	EP + Durva + Treme	EP + Durva + Treme	EP + Durva + Treme	EP + Durva + Treme	Durva	Durva + Treme*	Durva
Arm 2	EP + Durva	EP + Durva	EP + Durva	EP + Durva	Durva	Durva	Durva
Arm 3	EP	EP	EP	EP**			

* In the case of dose delay(s) more than one durvalumab + tremelimumab combination dose can be given post chemotherapy to ensure that up to 5 combination doses are administered in Arm 1.

** In Arm 3, EP can be given for an additional 2 cycles Q3W on Weeks 12 and 15 (ie, total 6 cycles post-randomization) if clinically indicated, at the investigator's discretion before patients enter Follow-up. Prophylactic cranial irradiation (PCI) can also be given at investigators' discretion. This does not alter the planned scan schedule Q8W starting at Week 12 for patients in Arm 3.

Durvalumab dose will be 1500 mg during chemotherapy and post-chemotherapy; tremelimumab dose will be 75mg during and post chemotherapy.

Note: Patients whose weight falls to 30 kg or below must receive weight-based dosing equivalent to 20 mg/kg of durvalumab and 1mg/kg tremelimumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg and 75 mg of tremelimumab.

EP Etoposide and platinum-based chemotherapy; Durva Durvalumab; PD Progressive disease; Treme Tremelimumab; Q3W Every 3 weeks; Q4W Every 4 weeks.

Safety Confirmation

An independent data monitoring committee (IDMC) comprised of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab ± tremelimumab in combination with platinum based chemotherapy at two early stages of enrolment. A step wise approach will be adopted. The initial safety review will take place when the first 30 patients (10 in each arm) have completed the 1st cycle of treatment and had 21 days of follow up. A second review will take place when an additional 30 patients (10 in each arm) have completed the 1st cycle of treatment and have had 21 days of follow up, making a total of 60 patients. At the time of 2nd review, it is expected that the initial 30 patients would have had at least 6 weeks of follow up, with some patients receiving much longer. These two reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned, or hold recruitment. The IDMC recommendation will be communicated to all sites when available.

In addition, the IDMC will meet approximately every 6 months thereafter to continue safety monitoring.

Statistical methods

The primary objective of this study is to assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP (Arm 1 vs. 3) and the efficacy of durvalumab + EP treatment compared with EP (Arm 2 vs 3) in terms of OS. OS is defined as the time from the date of randomization until death due to any cause.

The 2 primary endpoints of this study are OS (Arm 1 vs. 3) and OS (Arm 2 vs. 3). To control for type 1 error, a significance level of 1% will be used for the analysis of OS (Arm 1 vs. 3), and a significance level of 4% will be used for the analysis of OS (Arm 2 vs. 3). The study will be considered positive (a success) if either of the OS analysis results are statistically significant.

Secondary efficacy variables include PFS for durvalumab + tremelimumab + EP versus EP (Arm 1 vs. 3), PFS for durvalumab + EP versus EP (Arm 2 vs. 3), OS and PFS for durvalumab + tremelimumab + EP versus durvalumab + EP (Arm 1 vs. 2), objective response rate, the proportion of patients alive and progression free at 6 and 12 months from randomization and the proportion of patients alive at 18 months. PFS (per RECIST 1.1 as assessed by the site Investigator) is defined as the time from the date of randomization until the date of objective PD or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression. All endpoints related to tumor assessment are assessed by site Investigator.

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

There will be 2 data cut-off timepoints in the study. The interim analysis of OS will occur when approximately 318 OS events have occurred (60% maturity) in the durvalumab + tremelimumab + EP and EP treatment arms and approximately 318 OS events have occurred (60% maturity) in the durvalumab + EP and EP treatment arms (approximately 28 months after the first patient is randomized).

The data cut-off for the final analysis of OS (the second data cut-off) will occur when approximately 425 OS events have occurred across the durvalumab + tremelimumab + EP and EP treatment arms (80% maturity) and approximately 425 OS events have occurred across the durvalumab + EP and EP treatment arms (80% maturity). If the average true OS HR is 0.69, the study will have 89% power to demonstrate a statistically significant difference at the final analysis with a 2-sided 0.93% significance level (for an overall alpha of 1%) for the comparison of durvalumab + tremelimumab + EP versus EP (Arm 1 vs 3), and 96% power to demonstrate a statistically significant difference at a 2-sided 3.57% significance level (for an overall alpha of 4%) for the comparison of durvalumab + EP versus EP (Arm 2 vs 3); this translates to a 4.8-month benefit in median OS over EP (15.7 months vs 10.9 months).The smallest treatment difference that would be statistically significant is an average HR of 0.78 for durvalumab + tremelimumab + EP versus EP and 0.82 for durvalumab + EP versus EP. With a 15-month recruitment period and a minimum follow-up period of 27 months assumed, it is anticipated that this analysis will be performed 42 months after the first patient has been randomized.

At the time of each data cut-off, secondary efficacy endpoints will also be assessed. The complete testing strategy is described in Section 8.

OS will be analyzed using a stratified log-rank test (stratified for platinum-based therapy planned at Cycle 1 [cisplatin or carboplatin]). The effect of treatment will be estimated by the HR together with its corresponding confidence interval and p-value for the ITT population.

PFS, programmatically derived from site Investigator assessments, will be analyzed in the same way as OS above.

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

China data

Global recruitment will be complete once approximately 795 patients have been randomized. Once global enrollment is completed, recruitment will continue in China only. A total of up to 189 patients from China will be randomized (see Section 8.6 for details). To evaluate consistency as required by the CFDA, the efficacy and safety in the China cohort will be analyzed separately using the same statistical methods as for the global cohort analysis unless otherwise specified (see Section 8.6). Owing to late recruitment of patients in the expansion cohort, data cut-offs for the China cohort analyses may be different from global data cut-off to ensure appropriate evaluation. The analysis will be performed when the OS data from the China patients are of similar maturity, where significant clinical efficacy is established in the global cohort. Safety and tolerability will be summarized for the China Safety Analysis Set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization (ie, PFS rate at 12 months)
APF6	Proportion of patients alive and progression free at 6 months from randomization (ie, PFS rate at 6 months)
AST	Aspartate aminotransferase
AUC	Area under the drug concentration-time curve
AUC_{ss}	Area under the drug concentration-time curve at steady state
BP	Blood pressure
C	Cycle
C/D	Cycle/Day
CCTG	Canadian Cancer Trials Group
CD	Cluster of differentiation
CFDA	China Food and Drug Administration
CI	Confidence interval
CR	Complete response
CRF	Case report form (electronic/paper)
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
CXCL	Chemokine (C-X-C motif) ligand
DCO	Data cut-off
DCR	Disease control rate
DL1	Dose level 1
DLL3	Delta-like canonical Notch ligand 3
DLT	Dose-limiting toxicity

Abbreviation or special term	Explanation
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
ED	Extensive-stage disease
EORTC	European Organisation for Research and Treatment of Cancer
EP	Etoposide and platinum-based chemotherapy
ePRO	Electronic patient-reported outcome (device)
EQ-5D-5L	EuroQol 5-Dimension, 5-level health state utility index
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
Gx	Genetic Research
GMP	Good Manufacturing Practice
HbsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL	Interleukin
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)

Abbreviation or special term	Explanation
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LD	Limited-stage disease
LPLV	Last patient last visit
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor, and Welfare
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
OS18	Overall survival at 18 months after randomization
PCI	Prophylactic cranial irradiation
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
PFS2	Progression-free survival after subsequent anticancer therapy
PGIC	Patient’s Global Impression of Change
PK	Pharmacokinetic(s)
PNS	Paraneoplastic syndrome
PR	Partial response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-reported outcomes version of the CTCAE
Q2W	Every 2 weeks
Q3W	Every 3 weeks

Abbreviation or special term	Explanation
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
QLQ-C30 v3	30-item Core Quality of Life Questionnaire, version 3
QLQ-LC13	13-item Lung Cancer Quality of Life Questionnaire
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
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
STS	Soft-tissue sarcoma
TB	Total bilirubin
TIL	Tumor-infiltrating lymphocyte
TL	Target lesion
TMB	Tumor mutational burden
ULN	Upper limit of normal
US	United States
VT	Verbatim Term
WBDC	Web-Based Data Capture
WHO	World Health Organization
WT	Weight

1. INTRODUCTION

1.1 Background and rationale for conducting this study

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

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 disease (ED) 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 ED 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 ED 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 ED SCLC will relapse or experience disease progression (Clark and Ihde 1998). Therefore, the prognosis for patients with SCLC in general and particular ED SCLC is poor; the reported 2-year survival is only 5% and 5 years survival rate is less than 2% (Rossi et al 2012).

There are no large Phase III studies comparing cisplatin/etoposide and carboplatin/etoposide. A large meta-analysis of 4 studies (including >600 LD and ED patients), performed by Rossi et al 2012, showed similar efficacy between carboplatin- and cisplatin-containing regimens; median OS was 9.6 months for cisplatin and 9.4 months for carboplatin (hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.92 to 1.27; p=0.37). Objective response rate (ORR) was 67.1% and 66.0%, respectively (relative risk, 0.98; 95% CI, 0.84 to 1.16; p=0.83).

Several large phase III studies using EP as the comparator in this setting have consistently reported the median PFS between 4-6 months and median OS between 7-11 months (Slotman

et al 2015). Most recent published data on EP as control arm of a randomized phase III study reported median PFS in 1st line treatment of ED-SCLC as 4.4 months and median OS as 10.9 months (Reck et al 2016).

1.1.1 Immunotherapies

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

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate immune responses by delivering inhibitory signals to T cells through the PD-1 and CD80 receptors. PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor (Keir et al 2008) and to CD80 (Butte et al 2007). PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (eg, IFNγ) and can be found on both tumor cells (TC) and tumor infiltrating immune cells (IC). The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC, and protecting the tumor from immune elimination (Zou and Chen 2008). PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated (Butte et al 2007; Paterson et al 2011).

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28. In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015).

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012; Hirano et al 2005; Iwai et al 2002; Okudaira et al 2009; Topalian et al 2012; Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014; Rizvi et al 2015; Segal et al 2015). In addition, a high mutational burden eg, in bladder carcinoma (Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

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

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti-PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there is data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

1.1.2 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ) (Stewart et al 2015).

To date durvalumab has been given to more than 1800 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.2.1.3 and Section 6.5. Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4 cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of

cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (Tarhini and Kirkwood 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.2. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.4 Durvalumab + tremelimumab combination therapy

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

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

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

1.1.5 Rationale for conducting this study

ED SCLC is an aggressive malignancy, the prognosis remains poor despite favorable initial response to chemotherapy. Platinum-based chemotherapy has been the standard treatment for over 2 decades. Although patients have good responses to chemotherapy initially, almost all patients with ED-SCLC will relapse quickly. These facts indicate a significant unmet medical need. Novel therapies are urgently needed to improve clinical outcomes.

1.1.5.1 Rationale for the combination of durvalumab ± tremelimumab with chemotherapy

Nonclinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1 and CTLA-4) can have a positive effect on antitumor immunity. One potential strategy is to combine these nonredundant and potential synergistic single-agent immune checkpoint inhibitors, thereby producing an additive improvement in tumor response (Larkin

et al 2015, Postow et al 2015). 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 NSCLC, either used alone or in combination with chemotherapy. Preliminary efficacy data from Study D4190C00006 have demonstrated that durvalumab+tremelimumab is active and well tolerated. As of 15 April 2015, in 63 patients with at least 16 weeks of follow up, the objective response rate is 27%.

Recently the IMpower133 study was presented at the World Congress on Lung Cancer (Horn et al., September 2018). IMpower133 was a randomized placebo-controlled phase III study, comparing atezolizumab + etoposide/platinum (EP) with placebo + EP in frist line treatment of ED-SCLC. The study demonstrated a statistically significant improvement in OS with the combination of atezolizumab + etoposide/platinum (EP) compared to placebo + EP; the median OS was 12.3 months in the atezolizumab +EP group and 10.3 months in EP+ placebo group (hazard ratio for death, 0.70; 95% confidence interval [CI], 0.54 to 0.91; P = 0.007). The median progression-free survival was 5.2 months and 4.3 months, respectively (hazard ratio for disease progression or death, 0.77; 95% CI, 0.62 to 0.96; P = 0.02). The safety profile of atezolizumab plus carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents, with no new findings observed.

Nivolumab as monotherapy or in combination with ipilimumab (anti-CTLA-4 mAb) has also been investigated in relapsed SCLC in CheckMate 032 (Antonia et al 2016). In this study, nivolumab at 3mg/kg was tested as monotherapy, and nivolumab 1mg/kg + ipilimumab 3mg/kg, and nivolumab 3mg/kg+ipi 1mg/kg were assessed. The objective response rates reported were similar: 10%, 14% and 10%, respectively. Median survival data have also been recently reported of 4.4 months, 7.7 months and 6.0 months, respectively. Although the observed spectrum of toxicities was that expected for these agents, the fact that lower rates of Grade 3 or 4 toxicities were observed in the ipilimumab arm at 3mg/kg (compared to other tumor types) suggests that patients with SCLC tolerate CTLA4 blockade better.

The safety and efficacy of checkpoint inhibitors combined with chemotherapy have also been demonstrated across multiple tumor types. Data for durvalumab ± tremelimumab with standard platinum based chemotherapy in advanced cancers are being generated from 2 ongoing Phase I studies; an internal study D419SC00001 (n=6) and a phase Ib study (NCT02537418) run by the Canadian Cancer Trials Group (CCTG; n=111 as of an October 2016 cut-off). The combinations tested are tolerable and manageable; details on the safety profile found in these studies are summarized in Sections 1.2.2 and 1.3.2.4. Preliminary results from the CCTG study will be presented for the NSCLC cohorts in IASLC 2016; the overall objective response rate in NSCLC cohorts (n=24) was 52.9%.

In addition, KEYNOTE-021 Cohorts A-C is a multi-arm phase I study of pembrolizumab in combination with various chemotherapy regimens as 1st line treatment for NSCLC. The study has reported an objective response rate of 55% (Langer et al 2016).

In summary, the preliminary efficacy, safety, and tolerability data of durvalumab ± tremelimumab generated to date, together with early positive signals with other PD-1 and CTLA-4 checkpoint inhibitors in combination with chemotherapy support the development of these treatments in combination with EP chemotherapy in ED SCLC.

1.1.6 Study aim

This is a Phase III, randomized, open-label, comparative, multicenter, global study to determine the efficacy and safety of combining durvalumab ± tremelimumab with EP followed by durvalumab ± tremelimumab maintenance therapy versus EP alone as first-line treatment in patients with ED SCLC.

1.2 Rationale for study design, doses, and control groups

This is a Phase III, randomized, comparative study to assess the benefit-risk profile of adding immunotherapy to first-line chemotherapy versus current SoC of chemotherapy. Given the different treatment administration schedules and treatment durations, this study will use an open-label design.

1.2.1 Durvalumab and tremelimumab dose and treatment regimen justification

1.2.1.1 Durvalumab+ tremelimumab combination therapy dose rationale

The durvalumab + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (PD-L1 and CTLA-4 respectively), demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/Pharmacodynamics data

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

expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

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

Clinical data

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

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

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

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

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab Q4W

cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

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

All together, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination (equivalent to fixed doses of 1500 mg and 75 mg respectively) should be selected for further development.

Refer to the current durvalumab IB for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

1.2.1.2 Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [Q3W] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up (Schadendorf et al 2013).

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

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

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

The durvalumab + tremelimumab combination regimen will be administered for 4 doses Q3W in combination with chemotherapy followed by durvalumab monotherapy Q4W until disease progression. One additional combination dose will be administered post chemotherapy – see Section 1.2.2.

1.2.1.3 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

Data from Study D4190C00006 (phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. (For further information on PK observations in Study D4190C00006 , please see the current IB).

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen.

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUCss (4 weeks). Median Cmax,ss is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median Ctrough,ss is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20 mg/kg Q4W regimen.

1.2.1.4 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses = 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (Wang et al 2014). The population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al 2006, Wang et al 2009, Zhang et al 2012, Narwal et al 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg durvalumab (equivalent to 20 mg/kg) and a fixed dose of 75 mg tremelimumab (equivalent to 1 mg/kg) is included in the current study.

1.2.2 Rationale for proposed phase III dose and schedule

The dosing schedule proposed is aligned with the standard fixed dosing of 1500 mg durvalumab plus 75 mg tremelimumab for 4 cycles followed by durvalumab monotherapy (1500 mg), which is supported by efficacy and safety as well as tolerability data across multiple studies in multiple tumor types (see Section 1.2.1). To conform to the chemotherapy schedule in the study, we propose to use standard durvalumab+tremelimumab dose and ratio at a Q3W dosing interval, rather than the standard Q4W schedule.

The safety of a Q3W dosing schedule in combination with chemotherapy has been explored in an ongoing study D419SC00001 (described below), where tremelimumab is administered at 75 mg in combination with 1120 mg durvalumab Q3W followed by 1120 mg durvalumab Q3W. The combination has been declared tolerable and manageable (see below for more detail). The 1120 mg dose of durvalumab is the Q3W equivalent of the standard 1500 mg Q4W dose. The tremelimumab dose was not lowered proportionally to 56 mg as 75 mg is the lowest tested biologically effective dose.

In this study, we propose to use the phase III fixed dose of durvalumab, so this study will combine 75 mg tremelimumab with 1500 mg durvalumab Q3W in combination with chemotherapy. The relative increase in dose density of durvalumab (ie, 1500 mg Q3W instead of Q4W) is supported by the fact that toxicities attributable to durvalumab do not appear dose dependent, and pharmacokinetic modeling reveals no meaningful differences in drug levels between Q3W and Q4W dosing.

Supportive Clinical Data

The safety and tolerability data that support the proposed combination and schedule is based on two ongoing phase I/IB studies investigating the safety and tolerability of durvalumab + tremelimumab in combination with various chemotherapy regimens in solid tumors: an AstraZeneca internal study (D419SC00001) and CCTG study (NCT02537418).

<u>AstraZeneca Phase I Study (D419SC00001).</u>

This phase I study is evaluating the safety and tolerability of durvalumab + tremelimumab in combination with first-line chemotherapy regimens in patients with locally advanced or metastatic solid tumors. The tumor types originally included: ovarian/peritoneal/fallopian tube cancer, squamous cell carcinoma of the head and neck (SCCHN), triple-negative breast cancer (TNBC), small cell lung carcinoma (SCLC), and gastric/gastro-esophageal junction (GEJ) cancer.

In the SCLC cohort, durvalumab 1120 mg + tremelimumab 75 mg Q3W is given concurrently with carboplatin AUC 5 mg/mL/min and etoposide 100 mg/m^2 Q3W, followed by durvalumab 1120 mg monotherapy Q3W.

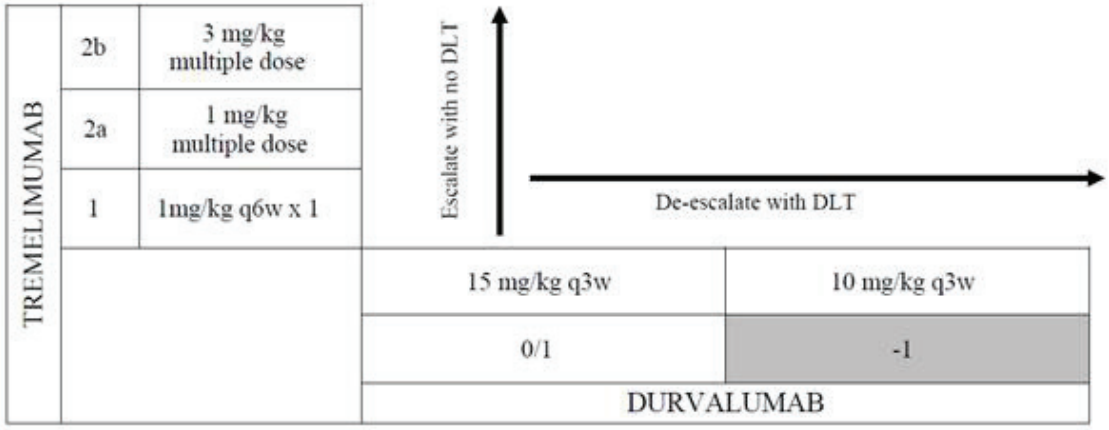
As of Dec 6, 2016, 6 patients with SCLC had completed 4 cycles of treatment. No DLT was reported during the first cycle of treatment (a 21-days period). One patient developed grade 4 hepatitis with elevation of ALT, AST and GGT at C5D1. Although the onset of this event was one day after the protocol defined DLT period of 4 cycles, it was considered as a DLT following discussion with investigator. The liver enzymes were normalized within 16 days after steroid use and was confirmed not to be a Hy's law case. As there was only one DLT reported in 6 patients, the safety profile of this combination with chemotherapy at Q3W schedule is declared tolerable and manageable.

<u>CCTG study (NCT02537418)</u>

This is an ongoing multi-center, phase I study of single or double immunotherapy (durvalumab ± tremelimumab) in combination with multiple standard platinum based chemotherapy regimens in patients with incurable advanced or metastatic cancer and is sponsored and conducted by the Canadian Clinical Trial Group (CCTG). Chemotherapy regimens assessed in the study include cisplatin+pemetrexed, cisplatin+gemcitabine, cisplatin+etoposide, carboplatin+pemetrexed, carboplatin+gemcitabine, nab-paclitaxel+carboplatin, and etopside+carboplatin at standard doses for each regimen.

The dose escalation and dose regimen are outlined below (Figure 2). Another dose level (DL3- durvalumab 1125mg + tremelimumab 56mg (maximum 6 doses of tremelimumab) Q3W with chemotherapy) was added after the protocol was initiated. A total of four dose levels of durvalumab ± tremelimumab are being assessed.

Figure 2 Study Schematic for CCTG Study



As of an October 2016 data cut off, a total of 111 patients have been dosed with 7 chemotherapy regimens across multiple tumor types; the majority of patients enrolled have been metastatic/advanced NSCLC patients (44%), followed by SCLC (16%) then bladder cancer (7%), and most have had no prior chemotherapy (71%). SCLC patients enrolled into the etoposide-carboplatin cohorts started IO treatment in cycle 3 of chemotherapy; all other chemotherapy regimens assessed the IO combination starting at cycle 1.

Overall, toxicities related to the chemotherapy core regimen appeared as expected in severity and frequency (See section 1.3.2.4 for more detail on the safety profile from this study). Overall, across all dose levels, there was no clear dose dependency in any of the reported AEs and there was no DLT reported per protocol defined criteria (DLT period of 21 days). Toxicities related to durvalumab and tremelimumab were also those expected for these agents, although a number of potential IO related toxicities such as diarrhea, skin rash, hepatic function changes or pneumonitis were difficult to differentiate from those reported for cytotoxic agents. As expected, there were more IO related toxicities reported for dose levels containing tremelimumab. In general, all regimens were tolerable and manageable at all dose levels. There was no discernible difference in the tolerability profile when IO treatment was

administered in cycle 1 (including SCLC patients) versus cycle 3 of chemotherapy for SCLC patients only.

In general, the overall safety profile from these two studies appears to be consistent with available safety and tolerability data for durvalumab in combination with tremelimumab.

PK Modelling

PK modelling has been carried out to predict the effect of switching from a Q4W regimen to a Q3W regimen for both durvalumab (1500 mg; 4 doses) and tremelimumab (75 mg; 4 doses) exposures. Results suggest that a Q3W regimen would yield similar exposures to Q4W; both durvalumab and tremelimumab are expected to yield a slightly higher Cmax and Cmin on a 3 week schedule, but a lower AUC. For durvalumab, Cmax values were 660 vs. 596 (µg/mL), Cmin, were 144 vs. 94 (µg/mL), and AUC was 5879 vs.6061 (µg/mL) for Q3W and Q4W schedule, respectively. For tremelimumab, Cmax is 26.1 vs. 25.1 (µg/mL), Cmin is 7.2 vs. 5.7 (µg/mL), and AUC is 267 vs. 289 (µg/mL), respectively for the Q3W vs. Q4W regimen.

Therefore, PK modeling suggests that a Q3W schedule does not impose a significant increased safety risk based on expected durvalumab and tremelimumab exposures.

Taken together, the totality of data provides sufficient safety data to support the combination of 1500mg durvalumab plus 75mg tremelimumab with chemotherapy. There is supportive safety data for the combination of 1120 mg durvalumab plus 75 mg tremelimumab Q3W x 4 doses followed by 1120 mg durvalumab Q3W from Study D419SC00001. The safety of the combination of 1125 mg durvalumab (Q3W) plus tremelimumab 75mg (multiple doses, Q6W) or 225mg (3 doses, Q6W) or 56mg (multiple doses, Q3W) with chemotherapy has been assessed in more than 100 patients in the CCTG Phase I trial. Clinical data from NSCLC patients in Study D4190C00006 suggest that increasing the dose of durvalumab has no significant impact on the safety and tolerability of the durvalumab and tremelimumab combination. In addition, PK modelling data suggest there will be a minimal impact on IP exposure if the standard doses (1500/75) are given on a Q3W regimen.

Additional dose of Tremelimumab

Patients in Arm 1 will receive additional one dose of durvalumab + tremelimumab post chemotherapy at week 16 if patient complete all 4 doses of durvalumab + tremelimumab during chemotherapy. The rationale to have an additional dose of tremelimumab after chemotherapy is based on the possibility that chemotherapy may limit the responsiveness of T cells to tremelimumab, and that tremelimumab given after chemotherapy will help control rapid progression that is inherent to the clinical course of SCLC, thereby sustaining the responses that may have been achieved during induction.

1.2.2.1 Safety confirmation of proposed doses

To better support the use of the 1500 mg durvalumab ±75mg tremelimumab Q3W in this study and to ensure safety and tolerability in this larger phase III study, a safety confirmation of the proposed dose and schedule will be conducted within the protocol by an independent

data monitoring committee (IDMC). A step wise approach will be adopted. An initial safety review will take place when the first 30 patients (10 in each arm) have enrolled and completed the 1st cycle of treatment and had 21 days of follow up. These 30 patients will be continued to be followed for long term safety. A second review will take place when an additional 30 patients (10 each arm) complete the 1st cycle of treatment and have had 21 days follow up, giving a total of 60 patients. At the time of this second review, it is expected that the initial 30 patients will have longer term follow up that may extend into the maintenance period. This safety review will be carried out by the IDMC in an unblinded fashion. The IDMC will make a recommendation on whether recruitment should continue, be modified or be held. The IDMC will continue to monitor the study conduct approximately every 6 months thereafter (see Section 6.10).

1.2.3 Rationale for control arm: standard care therapy

International guidelines (European Society for Medical Oncology [ESMO] and the National Comprehensive Cancer Network [NCCN]) currently recommend treatment with 4 to 6 cycles of platinum-based chemotherapy (EP), either cisplatin or carboplatin in combination with etoposide, without maintenance therapy for ED SCLC; this has been widely adopted in clinical practice across the world.

Although 6 cycles of EP have not been shown to be superior to 4 cycles in the overall population, 1 group did report a trend favoring 6 cycles of EP for an ED SCLC subgroup (Veslemes et al 1998). The use of 4 cycles of EP in the experimental arms (Arms 1 and 2) in this study is consistent with that observed in other trials combining platinum-based chemotherapy with investigational agents, particularly immunotherapies, to minimize the toxicity burden to patients. Patients in the control arm (Arm 3) can receive up to 6 cycles of EP; patients who demonstrate continued tumor volume reduction after 4 cycles of EP can continue with an additional 2 cycles of EP at investigators' discretion.

Cisplatin and carboplatin have indistinguishable clinical efficacy but are different in terms of cost and toxicity profiles. The selection of cisplatin or carboplatin in combination with etoposide is at the investigator's discretion, but must be in accordance with eligibility criteria, specifically inclusion 11, in Section 3.1. These agents are commonly used in ED SCLC and will be given as per the product label for the indication and the NCCN and ESMO guidelines (Früh et al 2013, Kalemkerian et al 2013).

- Etoposide: 80 to 100 mg/m^2 daily on Days 1 to 3 (total dose 300 mg/m^2) given Q3W
- Carboplatin: AUC 5-6 on Day 1 given Q3W
- Cisplatin: 75 to 80 mg/m^2 intravenous (IV) on Day 1 given Q3W

Prophylactic cranial irradiation (PCI) will be permitted for patients in Arm 3 only; this will be at the investigators' discretion as per SoC guidance for ED SCLC. PCI is not permitted for patients in Arms 1 and 2 due to the unknown risks of combining PCI with immunotherapies.

1.2.4 Rationale for endpoints

The primary objective of this study is to assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and the efficacy of durvalumab + EP treatment compared with EP in terms of OS. OS is the golden standard endpoint in oncology drug evaluation. The recent data from the IMpower133 study reinforces the importance of OS in this clinical setting.

PFS may serve as a surrogate endpoint for OS when differences between treatment arms are of sufficient magnitude and clinical importance (FDA Guidance 2011, Pazdur 2008). In certain settings, the utility of survival as an endpoint may potentially be confounded by subsequent therapies. Specifically, there are currently a number of molecules, that target the PD-1/PD-L1 pathway, which are in late-stage development to which patients with SCLC in the EP arm of this study may have access to upon progression. Nivolimab has recently received FDA approval for 3rd line treatment of ED SCLC. Access to these agents creates challenges in being able to fully characterize the effects of study treatment on OS if patients subsequently receive these immunotherapeutic agents. The comparison of the durvalumab + tremelimumab + EP and the durvalumab + EP arms will provide information as to the relative contribution of adding tremelimumab to the established benefit-risk profile of durvalumab + EP. This comparison is not currently included in the multiplicity-controlled statistical testing procedure because the proposed study is not powered for the comparison. However, the treatment difference will be summarized descriptively to evaluate the relative benefit-risk difference between the 2 experimental arms.

Antitumor activity, including the secondary endpoint of PFS, will be assessed per site investigators according to RECIST 1.1 guidelines.

Objective response rate is commonly used in oncology to directly measure treatment effect on the tumor. Other secondary efficacy endpoints of proportion of patients alive and progression free at 6 months from randomization (APF6 [PFS rate at 6 months]), proportion of patients alive and progression free at 12 months from randomization (APF12 [PFS rate at 12 months]) and overall survival at 18 months after randomization (OS18) will be examined to further evaluate the antitumor effect and survival benefit of durvalumab ± tremelimumab + EP compared with EP. APF6, APF12, and PFS will be assessed using site Investigator assessments according to RECIST 1.1.

The secondary endpoints of patient-reported symptoms and health-related quality-of-life (HRQoL) assessed using the EORTC QLQ-C30 v3 and QLQ-LC13 will show the overall benefits and toxicity of the treatment from the patient's perspective and will aid in assessing the benefit-risk evaluation. These PRO questionnaires are well-established instruments that have been used extensively in lung cancer clinical studies.

The PK and immunogenicity of durvalumab and tremelimumab are being examined to assess any potential impact on PK, pharmacodynamics, safety, and efficacy parameters. Biological samples will be used to explore potential biomarkers in tumor and serum that may influence pathogenesis, response, and clinical characteristics.

1.3 Benefit-risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with durvalumab and tremelimumab prior to the overall benefit-risk assessment.

1.3.1 Potential benefits

1.3.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first-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 durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥24 weeks follow-up, measurable disease at Baseline, and ≥1 follow-up scan or discontinued because of disease progression or death without any follow-up scan). Data from patients with SCLC in this study, although limited (n=19), showed a favorable disease control rate (DCR) of 26.3% when durvalumab was given 10 mg/kg Q2W.

In PD-L1 unselected patients, the ORR, based on investigator's assessment per RECIST 1.1, ranged from 0% in uveal melanoma to 20.0% in bladder cancer, and DCR at 24 weeks ranged from 4.2% in triple-negative breast cancer to 39.1% in advanced cutaneous melanoma. PD-L1 status was known for 383 of the 456 response evaluable patients. Across the PD-L1-positive tumors, ORR was highest (>10%) for bladder cancer, advanced cutaneous melanoma, and hepatocellular carcinoma (33.3% each); NSCLC (26.7%); and squamous cell carcinoma of the head and neck (18.2%). Moreover, in the PD-L1-positive subset, DCR at 24 weeks was highest (>10%) in advanced cutaneous melanoma (66.7%), NSCLC (36.0%), hepatocellular carcinoma and bladder cancer (33.3% each), and squamous cell carcinoma of the head and neck (18.2%).

1.3.1.2 Durvalumab + tremelimumab

Preliminary efficacy data from Study 6 have demonstrated that this combination is clinically active and well tolerated in NSCLC. As of 15 April 2015, 63 patients with at least 16 weeks of follow-up were evaluable for response across various durvalumab + tremelimumab dose regimens. Of these, 17 patients (27%) had a best overall response of PR, 14 patients (22%) had a best response of SD, 22 patients (35%) had PD, and 10 patients (16%) were NE. The ORR (confirmed and unconfirmed CR or PR) was 27%, and the DCR (CR, PR, or SD) was 49% as assessed by RECIST 1.1 (Eisenhauer et al 2009). In the 20-mg/kg durvalumab and 1-mg/kg tremelimumab Q4W cohort, a total of 5 of 11 patients were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with PR, 1 patient (20%) with SD, and 1 patient (20%) with PD.

As of 4 October 2015, preliminary efficacy data were available for 6 patients with SCLC treated in Study 10 (D4190C00010: a Phase I study of durvalumab in combination with tremelimumab in patients with advanced solid tumors) with the combination of durvalumab (20 mg/kg) and tremelimumab (1 mg/kg) administered Q4W for 4 doses, followed by durvalumab alone at a dose of 10 mg/kg Q2W for up to a total of 12 months. Among the

6 patients with SCLC, 1 unconfirmed PR and 1 SD were observed per investigator's assessment by RECIST 1.1.

Nivolumab as monotherapy, or in combination with ipilimumab (anti-CTLA-4 mAb), has also been investigated in relapsed SCLC in CheckMate 032 study (Antonia et al 2016). Nivolumab 3mg/kg as monotherapy and nivolumab 1mg/kg+ipilumab 3mg/kg, and nivolumab 3mg/kg+ipilimumab 1mg/kg were assessed. The objective response rates reported were similar, 10% 14% 10%, respectively. Median survival were 4.4 months, 7.7 months and 6.0 months, respectively (Antonia et al 2016).

1.3.1.3 Durvalumab ± tremelimumab with chemotherapy

Studies evaluating agents targeting PD-L1 or CTLA-4 in combination with chemotherapy have yielded encouraging results (see Section 1.1.5.1).

Durvalumab ± tremelimumab with standard platinum based chemotherapy in advanced cancers are being generated from an ongoing phase Ib study (NCT02537418) run by the Canadian Cancer Trials Group (CCTG). Preliminary results will be presented in IASLC 2016. Up to October 2016 cut off, a total of 111 patients have been dosed with various chemotherapy regimens and different tumor type. The overall objective response rate in the NSCLC cohort (n=24) was 52.9% (NSCLC data based on a data cut off of July 2016).

CheckMate 012 (NCT01454102) is a multi-arm Phase I study of nivolumab in combination with various anticancer agents or as monotherapy in chemotherapy-naïve patients with NSCLC. The result just published in the Journal Of Clinical Oncology showed the objective response rates for nivolumab 10 mg/kg plus gemcitabine-cisplatin, nivolumab 10 mg/kg plus paclitaxel-cisplatin, nivolumab 10 mg/kg plus paclitaxel-carboplatin, and nivolumab 5 mg/kg plus paclitaxel-carboplatin were 33%, 47%, 47% and 43% respectively; 24-week PFS rates were 51%, 71%, 38% and 51% respectively. On the basis of these results, the antitumor activity of first-line nivolumab in combination with platinum doublets is highly promising (Rizvi et al 2016).

In addition, the phase II KEYNOTE-021 study showed that the addition of pembrolizumab to standard-of-care carboplatin and pemetrexed followed by pembrolizumab for 2 years and indefinite pemetrexed maintenance therapy significantly improved the proportion of patients who achieved an objective response compared with carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy in patients with chemotherapy-naive, advanced non-squamous NSCLC (Langer et al 2016). In the study, 123 patients with stage IIIB/IV, chemotherapy-naive, nonsquamous NSCLC were randomized to receive four cycles of carboplatin and pemetrexed (500 mg/m^2 every three weeks), with or without 24 months treatment with pembrolizumab (200 mg every three weeks). 33 of 60 patients (55%; 95% CI 42, 68) in the pembrolizumab plus chemotherapy group achieved an objective response compared with 18 of 63 patients (29%; 18, 41) in the chemotherapy alone group (estimated treatment difference 26% [95% CI 9-42%]; p=0.0016).

The recently reported IMpower133 study compared atezolizumab in combination with EP chemotherapy in 1L ED-SCLC to placebo + EP. Result demonstrated a statistically significant improvement in OS with the combination of atezolizumab + EP compared to placebo + EP with median OS of 12.3 months in the atezolizumab + EP group compared to 10.3 months in placebo + EP group (hazard ratio for death, 0.70; 95% confidence interval [CI], 0.54 to 0.91; P = 0.007). The median progression-free survival was 5.2 months and 4.3 months, respectively (hazard ratio for disease progression or death, 0.77; 95% CI, 0.62 to 0.96; P = 0.02).

On the basis of these clinical data, the antitumor activity of PD-L1/CTLA-4 monoclonal antibodies in combination with first-line platinum-/taxane-based doublets is highly promising. Given the synergistic potential of durvalumab and tremelimumab, the combination of both these drugs with chemotherapy has the potential to further improve the response rates and response durability along with overall survival.

1.3.2 Overall Risks

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

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

1.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis and 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, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g. Guillain Barre syndrome, myasthenia gravis).

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

In monotherapy, clinical studies AEs at an incidence of ≥ 20% include events such as fatigue, cough, decreased appetite, dyspnea and nausea. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the

monotherapy data including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 6.9)

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

1.3.2.2 Tremelimumab

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

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

In monotherapy clinical studies, AEs reported at an incidence of $\geq$ 20% include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting and dyspnea. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab, and approximately 45% of patients experienced an SAE. Please see the current version of the IB for a detailed summary of monotherapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the tremelimumab program.

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

1.3.2.3 Durvalumab + tremelimumab

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

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20 mg/kg and a tremelimumab dose of 1 mg/kg) are similar to

those for durvalumab and tremelimumab monotherapy. Emerging data from Study D4190C00006, other studies evaluating the combination and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

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

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

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

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

1.3.2.4 Durvalumab ± tremelimumab with chemotherapy

There are two ongoing studies evaluating the safety and tolerability of combining durvalumab and tremelimumab with different chemotherapy regimens in patients with solid tumors, one is an AZ internal study (D419SC00001), the other is CCTG study NCT02537418– see Section 1.2.2).

In the AstraZeneca internal study (D419SC00001) 6 patients with SCLC were evaluable for safety at the time of this report. Common adverse events reported were neutropenia (6 pts), nausea (4 pts), decreased appetite (4 pts), rash (3 pts), diarrhea (2 pts) and pyrexia (2 pts). Diarrhea, skin rash were generally low grade, with the exception of one grade 3 erythroderma that responded to topical steroids. One patient with intermittent grade 1 diarrhea required steroid treatment and resolved. Cycle 4 was modified in this patient where IO was held and chemotherapy was dose reduced to 75% due to grade 4 neutropenia. Grade 3 and above events were febrile neutropenia (2 pts), platelet decrease (1 pt), and lung infection (1 pt) which were considered to be chemotherapy related, hepatitis (1 pt), and erythroderma (1 pt) which were considered to be immune related. Febrile neutropenia, lung infection, hepatitis were reported as SAE. 2 patients had Grade 3/4 lipase/amylase elevation at baseline and were considered not drug related; these were due to pancreatic metastasis at baseline confirmed by imaging. One patient died due to disease progression as primary cause and a secondary cause of lung infection. Two patients discontinued treatment due to immune related hepatitis and persistent skin rash. Two patients continue on active study treatment and are being followed up for long term safety.

In the CCTG study (NCT02537418) a total of 488 cycles have been administered up to the data cut off of October 2016 with 103 patients evaluable for non-hematologic adverse events.

Overall all patients experienced at least one AE (100%), 96% were considered by investigator as causally related to chemotherapy, 75% was considered as causally related to durvalumab and 55% was considered as causally related to tremelimumab. A total of 69 events (26% of all events) were CTC grade ≥3, regardless of causality. Of these, 20 events were considered by investigators as causally related to durvalumab treatment and 15 events were considered as causally related to tremelimumab treatment. SAE events were reported in 38% of patients (39/103) regardless of causality; 19% related to chemotherapy, 15% was considered by Investigator as related to durvalumab, while 11% was related to tremelimumab treatment. Note that some events considered related to durvalumab and tremelimumab treatment may be reported in the same patient(s).

Overall the common adverse events reported were grade 1-2 with the most commonly reported being fatigue (93%), nausea (72%), dyspnea (63%), constipation (59%), and cough (52%) regardless of causality. Most common chemotherapy related adverse events were fatigue (62%), nausea (58%), vomiting (32%), anorexia (28%), alopecia (27%) and peripheral sensory neuropathy (24%). Most common durvalumab-related adverse events were fatigue (42%), rash maculo-papular (17%), nausea (16%) and diarrhea (12%). Most common tremelimumab-related adverse events were fatigue (26%), rash maculo-papular (13%) and diarrhea (11%). Most common CTC grade ≥3 events were fatigue (11 events), thrombotic events (9), dyspnea (7), lung infection (7), diarrhea (7). Transient elevations in amylase and lipase were seen but no patient had clinical or radiological evidence of pancreatitis. TSH elevations of ≥5 x ULN were documented in 10 patients (10%) and 6 patients required initiation of thyroid replacement therapy on study. Three of these patients with elevated TSH had a previous history of hypothyroidism.

On all dose levels, dose delays of durvalumab were mostly for administrative reasons/patient request and neutropenia related to chemotherapy, while durvalumab ± tremelimumab were interrupted in 4 patients because of pneumonitis, colitis or rash.

Seven patients (6.7%) discontinued durvalumab ± tremelimumab due to adverse events: pneumonitis (3pts), hepatitis (1), myocarditis (1), hyperthyroidism (1) and limbic encephalitis (1).

There were seven deaths within 30 days of the last dose of protocol therapy. Two of these were considered to be at least possibly related to durvalumab or tremelimumab; one patient PPD had diarrhea, hyperthyroidism and myocarditis, which was steroid responsive but later declined active therapy. The cause of death has not yet been determined. The post mortem examination has not been reported. One patient PPD had confusion and possible encephalitis.

The 2 possibly related fatal cases are briefly described as follows:

Case Report No. PPD – An event of myocarditis (Grade 5) occurred in a 74 year old female with metastatic SCLC who on Cycle 1 Day 12 presented with s/s of fever, nausea, vomiting and decreased neutrophil count of 0.68 for which patient was eventually admitted. She developed diarrhea. CT abdomen showed liver metastasis, with inflammatory changes of duodenum suggestive of uncomplicated duodenitis or ulcer. Patient also developed acute renal failure and pulmonary edema. On Cycle 1 Day 16 the patient presented with s/s of Grade 4 heart failure and myocarditis as well as Grade 3 thyroiditis that initially responded to steroid administration. She was sent home only to be readmitted with weakness, fever, dizziness and dehydration. The patient's condition deteriorated despite steroids, supportive treatment (inotropic support, use of ace inhibitors) and eventually died. Preliminary autopsy report showed multiple metastases in the involved lungs (effusions), liver, and lymph nodes. Except for atherosclerosis, there were no evidence of myocardial infarction nor pulmonary emboli.

Case Report No. PPD. An event of limbic encephalitis (Grade 5) occurred in a 65 year old female with metastatic SCLC who on Cycle 2 Day 27 presented with s/s of limbic encephalitis (eg, cognitive decline, restlessness, agitation, EEG findings suggestive of encephalopathy, CSF findings of increased WBC and protein, MRI finding of no intracranial mass, and despite treatment with antibiotics, steroids, the patient eventually died. Confounding factors that may likely also provide alternative cause/explanation for this event include the following: 1) a possible paraneoplastic effect of underlying SCLC, 2) concomitant medications that included treatment with phenobarbitone and midazolam, 3) underlying diabetes mellitus for which patient had insulin/oral hypoglycemic treatment and 4) possible CNS infection.

Overall, toxicities related to the chemotherapy core regimen and to durvalumab and tremelimumab were as expected for these agents. In general, the combination of durvalumab plus tremelimumab with chemotherapy appears tolerable and manageable.

External clinical data also supports these findings. In a randomized Phase III study in patients with ED SCLC treated with etoposide-platinum ± ipilimumab, the overall incidence of treatment-related Grade 3/4 AEs was 48% for chemotherapy plus ipilimumab and 44% for chemotherapy plus placebo. The most common immune-related AEs in patients treated with chemotherapy + ipilimumab involved skin (rash and pruritus) and gastrointestinal tract (diarrhea) (Reck et al 2016). Furthermore, in the setting of single-IO + EP, the recently published IMpower133 study demonstrated that the safety profile of atezolizumab plus EP was consistent with the previously reported safety profile of the individual agents, with no new findings observed (Horn L et al., September 2018).

1.3.3 Overall benefit-risk assessment

There remains a significant unmet medical need for additional treatment options for patients with ED SCLC. Four or six cycles of platinum-based chemotherapy has been considered the standard treatment regimens for 2 decades; however, OS remains poor with a 2-year survival rate of 5% despite favorable initial responses. The vast majority of ED 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.

Treatment with durvalumab and/or tremelimumab has shown activity in several tumor types in a subset of patients deriving meaningful and durable benefit. Efficacy data for patients treated with durvalumab monotherapy have shown clinical activity across several tumor types. Preliminary data generated from patients with NSCLC treated with durvalumab + tremelimumab combination therapy have also shown early signs of clinical activity, and data from the literature indicate that the combination may act synergistically (Wolchok et al 2013). Thus, these agents may potentially offer benefit to this patient population. Also, as presented in Section 1.1.5.1, the studies evaluating agents targeting PD-L1 or CTLA-4 in combination with chemotherapy has yielded encouraging efficacy data, with a seemingly tolerable toxicity profile.

Therefore, the rationale for this study is supported by the available nonclinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, the activity seen with durvalumab alone and in combination with tremelimumab in a number of tumor types, the preliminary data on the efficacy and tolerability of the combination of PD-L1 or CTLA-4 with chemotherapy, and the strength of the scientific hypotheses evaluating the safety and tolerability of adding durvalumab ± tremelimumab to first-line standard platinum-based chemotherapy for the treatment of first-line ED SCLC.

Based on these considerations, the proposed treatments may have the potential to provide meaningful clinical benefit by generating durable clinical responses, thereby potentially extending survival. Therefore, the overall benefit-risk assessment supports the proposed study to evaluate the safety and tolerability of the combination of durvalumab and tremelimumab with standard platinum-based chemotherapy regimens.

1.4 Study design

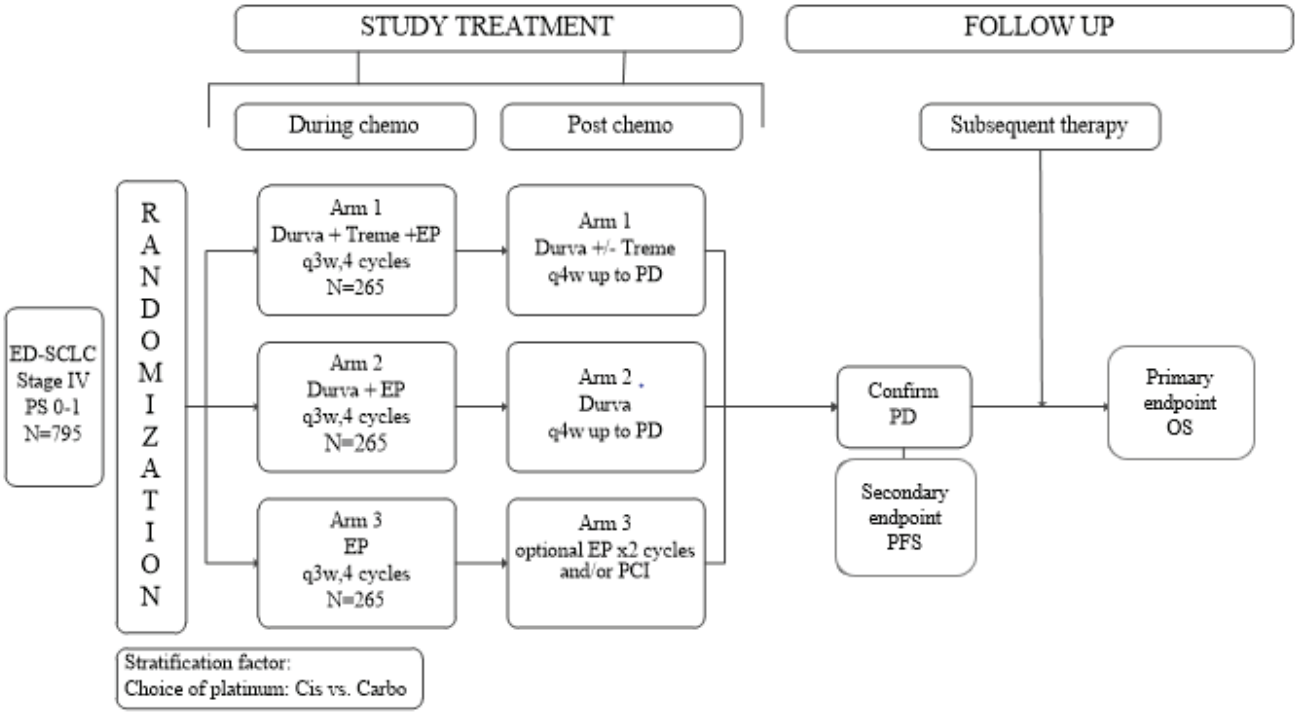
This is a Phase III, randomized, open-label, comparative, multicenter, global study to determine the efficacy and safety of durvalumab + tremelimumab + EP or durvalumab + EP versus EP chemotherapy as first-line treatment in patients with ED SCLC. A schematic diagram of the overall study design is shown in Figure 3, and a detailed study flow chart is shown in Figure 4.

This study will randomize approximately 795 eligible patients at sites worldwide. Once global enrollment of 795 patients is completed, recruitment will continue in China only. A total of up to 189 patients from China will be randomized (see Section 8.6 for detail).

Patients will be randomized in a 1:1:1 ratio in a stratified manner according to the planned platinum-based therapy for Cycle 1 (cisplatin or carboplatin) to receive treatment with durvalumab + tremelimumab + EP (Arm 1), durvalumab + EP (Arm 2), or EP (Arm 3). Cross over will not be permitted as part of this study. Doses and treatment regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 2 and Table 3.

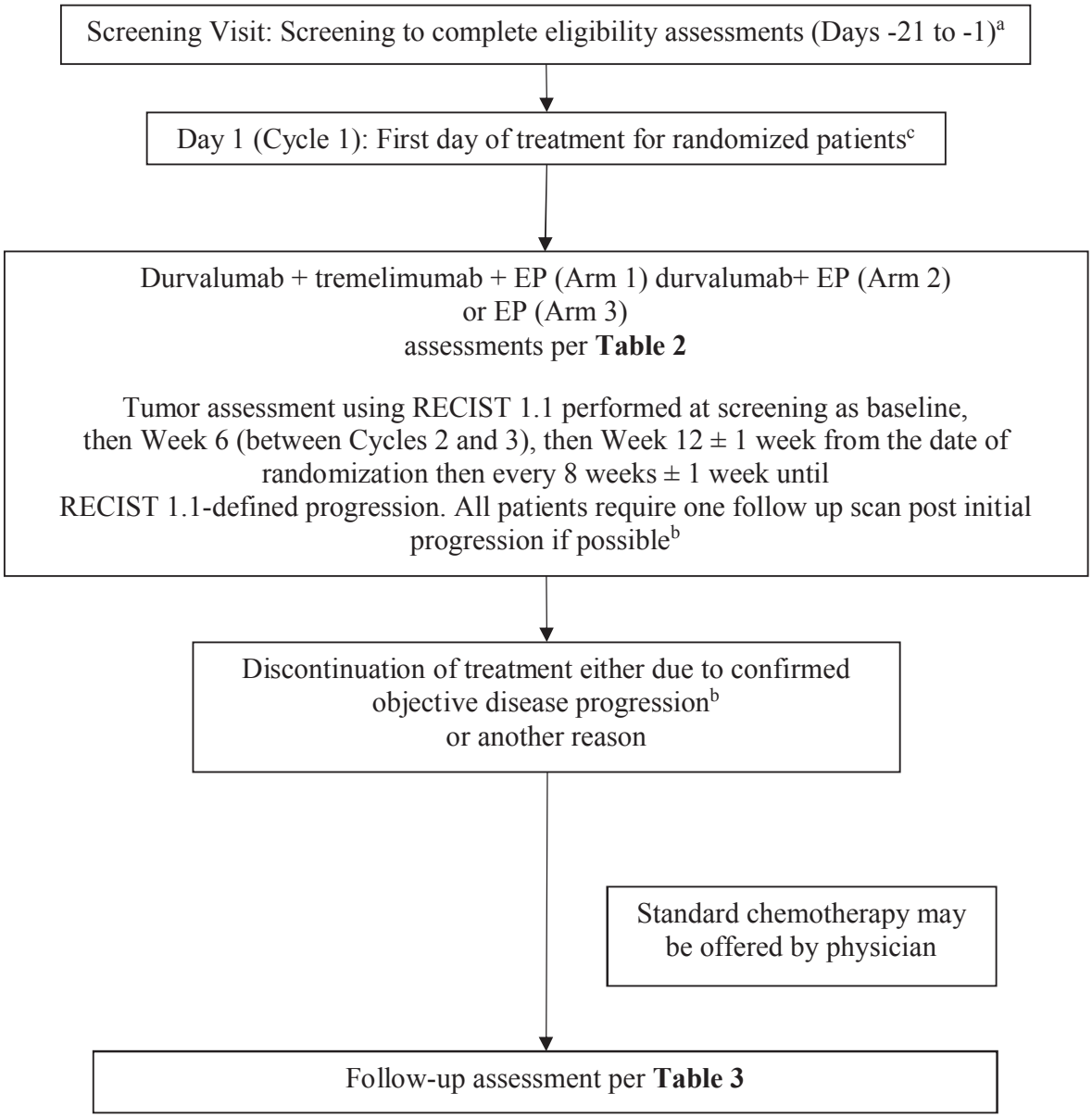
Tumor assessments will be performed at Screening as baseline with follow-ups at Week 6 ±1 week from the date of randomization, at Week 12 ±1 week and then every 8 weeks ±1 week until confirmed objective disease progression (please refer to Appendix E)

Figure 3 Overall study design



Durva Durvalumab; ED Extensive-stage disease; EP Etoposide and platinum-based chemotherapy; OS Overall survival; PCI prophylactic cranial irradiation; SCLC small-cell lung cancer; Treme Tremelimumab.
Note that only one dose of tremelimumab will be administered post chemotherapy in Arm 1 if a patient receives 4 combination doses during chemotherapy, ie, up to 5 durvalumab+tremelimumab combination doses in total – see Section 7.2.

Figure 4 Study flow chart



[a] Informed consent and completion of study procedures and baseline CT/MRI tumor assessment.
[b] A follow up scan is requested after every radiological PD on study where possible; this is irrespective of whether the PD needs to be confirmed or not as set out in Appendix E. As long as the patient is clinically stable, in the event of radiologic PD according to RECIST 1.1, an additional scan should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of radiologic PD (please refer to Appendix E)
[c] A window of up to 2 days is permitted between randomization and first dose of IP.

CR Complete response; Durva Durvalumab; EP Etoposide and platinum-based chemotherapy; OS Overall survival; PD Progressive disease; PR Partial response; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SCLC Small-cell lung cancer; SD Stable disease; Treme Tremelimumab.

2. STUDY OBJECTIVES

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

2.1 Primary objectives

Primary objective:	Outcome measures:
To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and durvalumab + EP treatment compared with EP in terms of OS	OS

EP Etoposide and platinum-based chemotherapy; OS Overall survival.

2.2 Secondary objectives

Secondary objectives:	Outcome measures:
To further assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and durvalumab + EP treatment compared with EP in terms of PFS, ORR, APF6 (PFS rate at 6 months), APF12 (PFS rate at 12 months), and OS18 (OS rate at 18 months)	PFS, ORR, APF6 and APF12 using site Investigator assessments according to RECIST 1.1 OS18
To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with durvalumab + EP in terms of PFS and OS	PFS using site Investigator assessments according to RECIST 1.1 OS
To assess the PK of durvalumab and durvalumab + tremelimumab	Concentration of durvalumab and tremelimumab in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling)
To investigate the immunogenicity of durvalumab and durvalumab + tremelimumab	ADA (confirmatory results: positive or negative; titers [ADA neutralizing antibodies will also be assessed])
To assess the effect of the treatment on changes in symptoms and health-related QoL using EORTC QLQ-C30 v3 and QLQ-LC13	EORTC QLQ-C30: symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Health-related QoL/functioning (physical function, role function, emotional function, cognitive function, social function, and global health status/QoL). EORTC QLQ-LC13: disease-related symptoms (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and other pain). Changes in WHO/ECOG performance status will also be assessed.

ADA Anti-drug antibody; AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomization (ie, PFS rate at 12 months); APF6 Proportion of patients alive and progression free at 6 months from randomization (ie, PFS rate at 6 months); ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EP Etoposide and platinum-based chemotherapy; OS Overall survival; OS18 Overall survival at 18 months after randomization; PFS Progression-free survival; PK Pharmacokinetic(s); QLQ-C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; WHO World Health Organization.

2.3 Safety objectives

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of durvalumab and durvalumab + tremelimumab in combination with EP treatment compared with EP	AEs; physical examinations; vital signs including blood pressure and pulse rate; electrocardiograms; and laboratory findings including clinical chemistry, hematology, and urinalysis

AE Adverse event; EP Etoposide and platinum-based chemotherapy.

2.4 Exploratory objectives

Exploratory objectives:	Outcome measures:
To further assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and to assess the efficacy of durvalumab + EP compared with EP in terms of PFS2	PFS2 using local standard clinical practice[a]
To investigate the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs, and/or safety parameters, and biomarkers, if deemed appropriate	A graphical and/or a data modelling approach will be used to analyze durvalumab PK exposure and the relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate.
To characterize EP PK when in combination with durvalumab and tremelimumab	Concentration of etoposide, cisplatin or carboplatin in blood
To explore the impact of treatment and disease on health care resource use	Health care resource use will be captured, including inpatient admissions, intensive care unit admissions, and length of stay in hospital
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To assess AEs by patient self-reporting of specific CTCAE symptoms	Collection of approximately 11 symptoms via the patient-reported outcomes version of the CTCAE (PRO-CTCAE)
To assess patients' overall impression of the change in their health status since the start of study treatment	PGIC item will be collected directly from patients.
To investigate the relationship between a patient's expression of select genes, for example IFN-γ, within the tumor microenvironment and efficacy outcomes with durvalumab ± tremelimumab and EP	Levels of gene expression, for example, IFN-γ, within the tumor microenvironment relative to efficacy outcomes (for example, APF6, APF12, PFS, and OS)
To investigate the relationship between a patient's PD-L1 expression and spatial distribution within the tumor microenvironment and efficacy outcomes with durvalumab ± tremelimumab and EP	Tumoral and/or infiltrating immune cell expression of PD-L1 and spatial distribution within the tumor microenvironment relative to efficacy outcomes (for example,APF6, APF12, PFS, and OS)
To investigate the relationship between a patient's level of DLL3 expression on tumor cells and efficacy outcomes with durvalumab ± tremelimumab and EP	Tumoral expression of DLL3 relative to efficacy outcomes (for example,APF6, APF12, PFS, and OS)

Exploratory objectives:	Outcome measures:
To investigate the relationship between a patient's TMB and/or somatic mutations/genomic alterations and efficacy outcomes with durvalumab ± tremelimumab and EP	Levels of TMB and somatic aberrations in tumor and/or plasma relative to efficacy outcomes (for example, APF6, APF12, PFS, and OS)
To explore potential biomarkers in residual biological samples (eg, tumor and blood), which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to durvalumab or durvalumab + tremelimumab treatment	Correlation of biomarkers with response to durvalumab or durvalumab + tremelimumab treatment and/or the progression of cancer
To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to study treatments and/or susceptibility to disease (optional)	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety, or response parameters observed in patients treated with durvalumab or durvalumab + tremelimumab and/or susceptibility to disease

AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomization (ie, PFS rate at 12 months); APF6 Proportion of patients alive and progression free at 6 months from randomization (ie, PFS rate at 6 months); CTCAE Common Terminology Criteria for Adverse Events; DLL3 Delta-like canonical Notch ligand 3; DNA Deoxyribonucleic acid; EQ-5D-5L EuroQol 5-Dimension, 5-level health state utility index; OS Overall survival; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Progression-free survival after subsequent anticancer therapy; PGIC Patient's Global Impression of Change; PK Pharmacokinetic(s); TMB Tumor mutational burden

[a] PFS2 will be defined as the time from the date of randomization to the earliest progression event subsequent to that used for the PFS endpoint or death.

A further objective, to fulfil China Food and Drug Administration (CFDA) requirements, is to evaluate the consistency in efficacy and safety among patients from China for benefit-risk assessment of durvalumab + tremelimumab in combination with EP treatment compared to EP and durvalumab + EP compared to EP.

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

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

3.1 Inclusion criteria

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

1. Male or female ≥18 years at the time of Screening. In Japan, patients must be aged ≥ 20 years at the time of Screening.

2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3. Histologically or cytologically documented extensive disease (American Joint Committee on Cancer Stage (7th edition) IV SCLC [T any, N any, M1 a/b]), or 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.

   – 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. Provision of an archived tumor tissue block (or at least 15 newly cut unstained slides) where such samples exist (refer to Section 5.5 and Laboratory Manual for details).

5. Patients must be considered suitable to receive a platinum based chemotherapy regimen as 1st line treatment for the ED-SCLC. Chemotherapy must contain either cisplatin or carboplatin in combination with etoposide.

6. Life expectancy ≥12 weeks at Day 1.

7. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 at enrollment.

8. Body weight >30 kg.

9. 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.

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:

- Hemoglobin ≥9.0 g/dL.
- Absolute neutrophil count ≥1.5 × 10^9/L (use of granulocyte colony-stimulating factor is not permitted at screening).
- Platelet count ≥100 × 10^9/L.
- Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physicians.
- 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 on cisplatin and >45mL/min for patients on carboplatin, as determined by Cockcroft-Gault (using actual body weight):

  Males:

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

  Females:

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

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).

3.2 Exclusion criteria

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

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

2. Previous IP assignment in the present study.

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. Participation in another clinical study with an IP during the last 4 weeks.

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

6. Any history of radiotherapy to the chest prior to systemic therapy or 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. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer related conditions (eg, hormone replacement therapy) is acceptable.

8. 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.

9. History of allogeneic organ transplantation.

10. 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.

11. 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

12. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, interstitial lung disease, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, 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.

13. History of another primary malignancy except for

    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease

14. History of leptomeningeal carcinomatosis.

15. History of active primary immunodeficiency.

16. 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.

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

18. 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.

19. 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 monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy.

20. Known allergy or hypersensitivity to durvalumab, tremelimumab, etoposide, carboplatin, cisplatin, or any of their excipients

21. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

For patients who have consented to Genetics Sample the following exclusion criteria apply:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection

For procedures for withdrawal of incorrectly enrolled patients, see Section 3.4.

3.3 Patient enrollment and randomization

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

At Screening (Days -21 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. Obtain a unique 7-digit enrollment number (E-code), through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in the following format (ECCNNXXX: CC being the country code, NN being the center

number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

3. Determine patient eligibility. See Section 3.1 and Section 3.2.

4. Obtain signed informed consent for genetic research study (optional).

5. Choose platinum agent that the patient would receive in cycle 1 (based on the most appropriate option for the patient). The information will be recorded in the IVRS/IWRS system at randomization.

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 randomization of the patient.

At randomization, once the patient is confirmed to be eligible, the investigator or suitably trained delegate will obtain a unique randomization number via the IVRS/IWRS. Numbers will start at 001 and will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 3 treatment arms.

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

Patients will begin treatment on Day 1, although a window of up to 2 days is permitted between randomization and first dose of IP. Patients must not be treated unless all eligibility criteria have been met.

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

3.4 Procedures for handling incorrectly enrolled or randomized patients

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

When a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on treatment, the investigator should inform the 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.

3.5 Methods for assigning treatment groups

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

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IVRS/IWRS will provide the kit identification number to be allocated to the patient at the randomization visit and following treatment visits.

3.6 Methods for ensuring blinding

Not applicable; this study is not blinded.

3.7 Methods for unblinding

Not applicable; this study is not blinded.

3.8 Restrictions

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

1. Female 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 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. 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 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab

monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

– 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).

- **Patients in the SoC (Arm 3) group:** Follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the SoC (Arm 3) group.

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

Barrier/intrauterine methods	Hormonal methods
Copper T intrauterine device	Etonogestrel implants: eg, Implanon or Norplan
Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	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. **PCI** will not be permitted in Arms 1 and 2 due to the unknown effects of combining PCI with immunotherapies. It will be permitted in Arm 3 if clinically indicated at investigators' discretion.

4. **All patients:** Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

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

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP (durvalumab + tremelimumab + EP, durvalumab + EP, or EP) if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 3.10.2).

- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.

- An AE that meets criteria for discontinuation as defined in the Toxicity Management Guidelines or as defined in the local prescribing information for the SoC agent.

- 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.
- Confirmed PD, as per investigator assessment.

3.9.1 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 6). The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter the Follow-up period (see Table 3).

Patients who permanently discontinue drug for reasons other than confirmed objective RECIST disease progression should continue to have RECIST scans performed Q6W ± 1 week for the first 12 weeks, then Q8W ± 1 week until confirmed objective disease progression/death (whichever comes first) as defined in Table 3.

If a patient is discontinued for unconfirmed progression then the patient should also continue to have RECIST scans performed Q6W ± 1 week for the first 12 weeks, then Q8W ± 1 week until confirmed objective disease progression or until death (whichever comes first) as defined in Table 3.

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

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in Table 3 as an alternative.

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

If a patient is withdrawn from study, see Section 3.11.

3.10 Criteria for withdrawal

3.10.1 Screen failures

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

3.10.2 Withdrawal of the informed consent

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

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

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

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

- all further participation in the study including any further follow up (eg, survival contact telephone calls)
- withdrawal to the use of any samples (see Section 5.5.4).

3.10.2.1 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 (see Section 9.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

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

- Lost to follow-up: site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The SURVIVE module will be updated.)
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available 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.)

3.11 Discontinuation of the study

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

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

In addition, the study may be stopped based on the findings of the interim safety analysis conducted by the Independent Data Monitoring Committee (IDMC) (see Section 6.10).

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and treatment periods in this study are presented in Table 2 and the procedures for the follow-up period are presented in Table 3. Patients treated in Arms 1 and 2 who continue beyond week 20 will continue with all week 20 assessments defined in Table 2 until confirmed progression or termination of treatment (Table 2). Patients who discontinue or complete treatment (ie, patients in arm 3 who complete 4 cycles of chemotherapy) will follow assessments as defined in Table 3. All patients must follow the scan schedule which is at baseline, week 6±1 week, week 12±1 week and Q8W ±1 week from randomization thereafter until confirmed PD. Follow up visits should be planned to align to this scan schedule where possible.

For all treatment arms

- PRO and tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (not the date of therapy).
- AstraZeneca requests that at least one subsequent scan is acquired and sent to AstraZeneca-appointed imaging Contract Research Organization after each initial progression event for all patients, across all arms of the study if possible.
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc required for dosing should be performed within 3 days prior to dosing.

For durvalumab monotherapy or durvalumab + tremelimumab combination arms

- Patients may delay dosing under certain circumstances:
  - Dosing may be delayed per the Toxicity Management Guidelines, due to either an immune or a non-immune-related AE. Note: 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. Communication with the Sponsor for questions is welcomed.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Dosing intervals of subsequent cycles (during chemotherapy interval is 21 days, post chemotherapy interval is 28 days) may be shortened as clinically

feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days during chemotherapy and less than 22 days after chemotherapy, based on the half-lives of durvalumab and tremelimumab (see current IBs for durvalumab and tremelimumab).

Standard of Care Arm:

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

Table 2 Schedule of assessments for Arms 1, 2, and 3 Treatment period

		During Chemotherapy 1 cycle = 3 weeks								**Post-Chemotherapy** 1 cycle = 28 days			
	Screening	**C1**	**C1/D8**	**C2**	**C2/D8**	**C3**	**C3/D8**	**C4**	**C4/D8**	**C5**	**C6**	**C7 to PD (4 weeks)**	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20**	
Day	**-21 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days) unless a dose delay is needed for toxicity management	**NA**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Informed consent for study procedures including biomarker sample collection	X												4.1, 10.4
Consent for genetic sample and analysis (optional)	X												Appendix C Genetic Research
Study procedures													
Physical examination (full)	X												5.2.2
Targeted physical examination (based on symptoms)		X	X	X	X	X	X	X	X	X	X	X	5.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse rate)[a]	X	X	X	X	X	X	X	X	X	X	X	X	5.2.4
12-lead ECG[b]	X	As clinically indicated											5.2.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Demography, including baseline characteristics and tobacco use	X												4.1
Eligibility criteria	X	X											3.1, 3.2

		During Chemotherapy 1 cycle = 3 weeks								**Post-Chemotherapy** 1 cycle = 28 days			
	Screening	**C1**	**C1/D8**	**C2**	**C2/D8**	**C3**	**C3/D8**	**C4**	**C4/D8**	**C5**	**C6**	**C7 to PD (4 weeks)**	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20**	
Day	**-21 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days) unless a dose delay is needed for toxicity management	**NA**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Laboratory assessments													
Clinical chemistry	X[c]	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Hematology	X[c]	X	X	X	X	X	X	X	X	X	X	X	5.2.1
TSH, free T_3, and free T_4[d]	X	X		X		X		X		X	X	X	5.2.1
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Hepatitis B and C and HIV	X												5.2.1
Pregnancy test[e]	X	X		X		X		X		X	X	X	5.2.1
Efficacy assessments													
Tumor evaluation (CT or MRI) (RECIST 1.1) [f]	X[g]	RECIST 1.1 tumor assessments should be performed at Week 6 ±1 week, at Week 12±1 week then every 8 weeks ±1 week relative to the date of randomization until RECIST 1.1-defined progression. All patients require one follow up scan post initial progression where possible.											5.1
PK													
Durvalumab PK sample (serum; Arms 1 and 2 only)		X[i]		X[j]						X[j]			5.4.1
Tremelimumab PK sample (serum; Arm 1 only)		X[i]		X[j]						X[j]			5.4.1
Etoposide PK sample (serum or plasma; selected sites only)[k]		X											5.4.1

	Screening	During Chemotherapy 1 cycle = 3 weeks								Post-Chemotherapy 1 cycle = 28 days			
		C1	**C1/D8**	**C2**	**C2/D8**	**C3**	**C3/D8**	**C4**	**C4/D8**	**C5**	**C6**	**C7 to PD (4 weeks)**	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20**	
Day	**-21 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days) unless a dose delay is needed for toxicity management	**NA**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Carboplatin or cisplatin PK sample (serum or plasma; selected sites only)[k]		X											5.4.1
Monitoring													
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	5.2.6
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	6.3.1
Drug accountability		X		X		X		X		X	X	X	7.6
IP administration (Interval between 2 consecutive doses cannot be less than 21 days during chemotherapy and less than 22 days after chemotherapy)													
Arm 1: durvalumab + tremelimumab + EP													
Durvalumab[l,m]		X[z]		X		X		X		X	X	X[n]	7.2.1
Tremelimumab[l,m,n]		X[z]		X		X		X			X		7.2.1
Etoposide[o,p]		X[z]		X		X		X					7.2.1
Carboplatin or cisplatin[o,q]		X[z]		X		X		X					7.2.1
Arm 2: durvalumab + EP													
Durvalumab [l,m]		X[z]		X		X		X		X	X	X[n]	7.2.1
Etoposide [o,p]		X[z]		X		X		X					7.2.1
Carboplatin or cisplatin [o,q]		X[z]		X		X		X					7.2.1

		During Chemotherapy 1 cycle = 3 weeks								Post-Chemotherapy 1 cycle = 28 days			
	Screening	**C1**	**C1/D8**	**C2**	**C2/D8**	**C3**	**C3/D8**	**C4**	**C4/D8**	**C5**	**C6**	**C7 to PD (4 weeks)**	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20**	
Day	**-21 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days) unless a dose delay is needed for toxicity management	**NA**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Arm 3: EP (4-6 cycles)													
Etoposide [p]		X[z]		X		X		X[r]					7.2.1
Carboplatin or cisplatin [q]		X[z]		X		X		X[r]					7.2.1
PRO assessments timing													
EORTC QLQ-C30 v3, EORTC QLQ-LC13, EQ-5D-5L, and PRO CTCAE [s,t]	X	X		X		X		X		X	X	X	5.3.1.1, 5.3.1.2, 5.3.1.3, 5.3.1.5
Patient's Global Impression of Change (PGIC)[s,u]				X		X		X		X	X	X	5.3.1.4
Other laboratory assessments and assays													
Immunogenicity assessment for durvalumab and tremelimumab (ADA sampling to identify ADA responses in patient circulation) [v]		X								X[w]			5.4.2
Mandated archival/diagnostic tumor sample <3 years old, where available. Samples should only be sent for patients who are enrolled and randomized	X												5.5.1

		During Chemotherapy 1 cycle = 3 weeks								Post-Chemotherapy 1 cycle = 28 days			
	Screening	**C1**	**C1/D8**	**C2**	**C2/D8**	**C3**	**C3/D8**	**C4**	**C4/D8**	**C5**	**C6**	**C7 to PD (4 weeks)**	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20**	
Day	**-21 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days) unless a dose delay is needed for toxicity management	**NA**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**For details see Section**
Plasma sample for tumor mutational burden (TMB)		X (pre-dose)											
Gx sample (optional DNA element for long-term storage/future use)[x]		X											Appendix C Genetic Research
Health economics measurements													
Hospital resource use module (HOSPAD)[y]	X	X		X		X		X		X	X	X	5.3.3

[a] Body weight is recorded along with vital signs.
[b] Any clinically significant cardiovascular findings require a confirmatory ECG.
[c] Screening laboratory assessments must be obtained within 7 days prior to Day 1. If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion).
[d] Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[e] Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable.
[f] RECIST 1.1 assessments will be performed on images from CT scans (preferred) or MRI scans, each preferably with IV contrast, of the chest and abdomen (including liver and adrenal glands). Additional anatomy should be scanned based on signs and symptoms of individual patients at Baseline and Follow-up. A follow up scan is requested after every radiological PD on study where possible; this is irrespective of whether the PD needs to be confirmed or not as set out in Appendix F. As long as the patient is clinically stable, in the event of radiologic PD according to RECIST 1.1, an additional scan should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of radiologic PD (please refer to Appendix F). If an unscheduled assessment was performed and the patient has not reached PD, every attempt should be made to perform the subsequent assessments at their next scheduled visit.
[g] Patient's diagnostic scan may be used as a baseline scan if taken within 28 days of randomization and in accordance with the requirements outlined in Appendix F.
[h] Patients will have scans done Q6W for the first 12 weeks, and then Q8W thereafter (relative to the date of randomization) until confirmed objective disease progression. Patients with confirmed PD who continue to receive durvalumab ± tremelimumab combination therapy at the discretion of the Investigator (following consultation with AstraZeneca) can receive their assigned treatment until no longer having clinical benefit.

[i] PK sampling should be performed within 10 minutes of the end of infusion.

[j] Both PK samples are to be taken before the tremelimumab infusion at Cycle 2, and this will be before the durvalumab infusion in Cycle 5.

[k] Selected sites only: Etoposide PK sample – collect at the end of infusion, 6 hours post infusion, and 24 hours post infusion. Cisplatin PK sample – collect at the end of infusion, 1 hour post infusion, and 3 hours post infusion. Carboplatin PK sample – collect at the end of infusion, 6 hours post infusion, and 24 hours post infusion.

[l] In cycles including tremelimumab, tremelimumab will be administered first followed by durvalumab. Durvalumab infusion will start approximately 60 minutes (maximum 2 hours) after the end of tremelimumab infusion. The 60-minute observation period is recommended after the first infusion of both tremelimumab and durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle involving tremelimumab and durvalumab, subsequent infusion observation periods can be undertaken at the investigator's discretion (30 minutes after each infusion is suggested).

[m] Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion).

[n] Durvalumab treatment is continued until PD. Patients with confirmed PD who continue to receive durvalumab ± tremelimumab combination therapy at the discretion of the Investigator (following consultation with AstraZeneca) can receive their assigned treatment until no longer having clinical benefit

[o] The immunotherapy agents are infused first followed by the etoposide + cisplatin/carboplatin regimen

[p] Infuse over 0.5 to 1 hour.

[q] If cisplatin, infuse over 1 to 2 hours. If carboplatin, infuse over 0.5 to 1 hour.

[r] EP Q3W up to 4 doses; extension into Weeks 12 and 15 is at the investigators' discretion. Note: tumor evaluation at Week 12 ± 1 week and Q8W thereafter and PRO collection Q4W until PD are required irrespective of the number of cycles of EP given

[s] For the PRO collection, the research nurse or study coordinator should ensure that the patient completes the questionnaire prior to any other study procedures and before discussion of PD to avoid introducing bias to the patient's responses to the questions. The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.

[t] PRO-CTCAE will only be administered in countries where a linguistically validated version exists.

[u] PGIC will only be administered after the patient has received started to receive treatment.

[v] ADA for tremelimumab will be assessed for Arm 1 patients only; ADA for durvalumab will be performed for Arm 1 and 2 patients only.

[w] A sample to look for antibodies to tremelimumab will be taken 90 days ± 7 days after last dose of tremelimumab

[x] The sample for genetic research will be obtained at Day 1 pre-dose (at or after randomization). If for any reason the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study, after obtaining signed optional informed consent.

[y] The site should complete the HOSPAD form at every scheduled and unscheduled clinic visit up to and including the study treatment discontinuation follow-up visit. If the patient discontinues study treatment for reasons other than RECIST 1.1 assessed PD, the HOSPAD form should continue to be completed until PD has been confirmed.

[z] A window of up to 2 days is permitted between randomization and first dose of IP. Randomization on Friday and dosing on Monday will be accepted.

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

ADA Anti-drug antibody; AE Adverse event; C Cycle; CR Complete response; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; D Day; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EP Etoposide and platinum-based chemotherapy; EQ5D-5L EuroQol 5-dimension, 5-level health state utility index; HIV Human immunodeficiency virus; HOSPAD Hospital resource use module; IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; NA Not available; PD Progressive disease; PGIC Patient's Global Impression of Change; PGx Pharmacogenetic research; PK Pharmacokinetic(s); PR Partial response; PRO Patient-reported outcomes; PRO-CTCAE Patient-reported outcomes version of the CTCAE; Q3W Every 3 weeks; Q4W Every 4 weeks; QLQ C30 v3 30 item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 3 Schedule of assessments for patients who have completed/discontinued treatment with durvalumab + tremelimumab + EP, durvalumab + EP, or EP

	Time since last dose of IP								
	Day (±3)	Months (±1 week)							Every 2 months (±2 weeks)
Evaluation	**28**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	
Physical examination (full)[a]	X								
Vital signs (temperature, respiratory rate, blood pressure, and pulse rate)	X								
Weight	X	X	X		X				
Pregnancy test[b]	X	As clinically indicated							
AE/SAE assessment[c]	X	X	X						
Concomitant medications	X	X	X						
WHO/ECOG performance status[d]	At timepoints consistent with tumor assessments, at 30, 60, and 90 days and at initiation of subsequent anticancer therapy								
Subsequent anticancer therapy[e]	To be checked and recorded on every visit								
Survival status[f]		X	X	X	X	X	X	X	X
Hematology[o]	X	X	X						
Clinical chemistry	X	X	X						
TSH, free T_3, and free T_4 [g]	X	X	X						
Immunogenicity assessment (Durvalumab and Tremelimumab ADA sampling to identify ADA responses in patient circulation)[h]			X[i]						
EORTC QLQ-C30 v3[j], EQ-5D-5L[j], EORTC QLQ-LC13[j], PRO-CTCAE [j,k], and PGIC[j]	Q4W until PD, then on Day 28 post PD, then 2 months post PD and then Q8W (±2 weeks) until second progression/death (whichever comes first)								
Hospital resource use module (HOSPAD)[l]	X								
Tumor assessment (CT or MRI)[m]	RECIST 1.1 tumor assessments should be performed at Week 6 ±1 week, at Week 12±1 week then every 8 weeks ±1 week relative to the date of randomization until RECIST 1.1-defined progression. All patients require one follow up scan post initial progression if possible.								

	Time since last dose of IP								
	Day (±3)	Months (±1 week)							Every 2 months (±2 weeks)
Evaluation	**28**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	
Second progression assessment[n]	Patients who discontinue study drug following progression will be assessed every 12 weeks for a second progression (using the patient's status at first/confirmed progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death (using the patient's status at first progression as the reference for assessment of second progression).								

[a] Physical examinations are described in Section 5.2.2.
[b] Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable.
[c] AEs and SAEs will be collected until 90 days following discontinuation of study treatment (ie, the last dose of durvalumab, durvalumab + tremelimumab or EP)
[d] WHO/ECOG performance status should also be collected at other site visits that the patient attends; if appropriate, site staff are available to collect such information. In addition, WHO performance status should be provided when information on subsequent anticancer therapy is provided, where possible.
[e] Details of any treatment for SCLC (including surgery) after the last dose of study treatment must be recorded in the eCRF
[f] Patients may be contacted in the week following data cut-off to confirm survival status. Details of any treatment for SCLC (including surgery) after the last dose of study treatment must be recorded in the eCRF. Every effort should be made to contact patients by telephone to follow and record survival status. Survival assessments may continue per protocol (every 2 months) post the primary analysis of OS unless instructed otherwise by AstraZeneca
[g] Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[h] ADA for tremelimumab will be assessed for Arm 1 patients only; ADA for durvalumab will be performed for Arm 1 and 2 patients only.
[i] A sample to look for antibodies to tremelimumab will be taken 90 days ± 7 days after last dose of tremelimumab.
[j] For the PRO data collection, the research nurse or study coordinator should ensure that the patient completes the questionnaire prior to any other study procedures and before discussion of PD to avoid introducing bias to the patient's responses. The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.
[k] PRO-CTCAE will only be administered in countries where a linguistically validated version exists.
[l] The site should complete the Hospital Admission (HOSPAD) form at every scheduled clinic visit up to and including the study treatment discontinuation follow-up visit. If the patient discontinues study treatment for reasons other than RECIST 1.1 assessed PD, the HOSPAD form should continue to be completed until PD has been confirmed.
[m] Only for patients yet to progress, RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including liver and adrenal glands). Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients. A follow up scan is requested after every radiological PD on study where possible; this is irrespective of whether the PD needs to be confirmed or not as set out in Appendix F. As long as the patient is clinically stable, in the event of radiologic PD according to RECIST 1.1, an additional scan should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of radiologic PD (please refer to Appendix F).If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomization).
[n] For patients who discontinue their assigned IP following confirmed PD, available readings of CT/MRI from local practice will be collected from the patients' medical charts while information on subsequent anticancer treatment and/or PFS2 is collected.
[o] For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed as clinically indicated.

4.1 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 or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening 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 21 days of randomization (except if using a patient's diagnostic scan which may be used as a baseline scan if taken within 28 days of randomization and in accordance with the requirements outlined in Appendix E). All patients will be asked to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) where available. This consent is included in the main patient informed consent form (ICF).

Screening/baseline evaluations may be performed over more than 1 visit.

The timing of vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Table 2.

4.2 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. The timing of the vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Table 2.

- Patients in Arm 3 only:

Patients who receive additional cycles of EP and/or PCI at investigators' discretion will be expected to follow the assessment schedule in Table 3 after 4 cycles of EP; additional visits or scans due to the optional extension of EP or PCI will be recorded as unscheduled visits/assessments.

4.2.1 Safety Confirmation Period

This applies to the first 60 patients randomised to the study and will be split into two parts; an unblinded safety review carried out by the IDMC will be conducted after the initial 30 patients have had a minimum of 21 days follow up and again after an additional 30 patients have been randomised and had 21 days of follow up (see Section 6.10.1 for details). All procedures will follow the same assessment schedule as for the treatment period (Table 2).

4.3 Follow-up period

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see Table 3).

Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed Q6W ± 1 week for the first 12 weeks (relative to the date of randomization), and then Q8W ± 1 week thereafter until confirmed objective disease progression/death (whichever comes first) as defined in Table 3.

If a patient is discontinued for unconfirmed progression then the patient should also continue to have RECIST scans performed Q6W ± 1 week for the first 12 weeks (relative to the date of randomization), and then Q8W ± 1 week thereafter until confirmed objective disease progression or until death (whichever comes first) as defined in Table 3.

All procedures to be conducted during the Follow-up period will be performed according to the assessment schedule (see Table 3).

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

All patients will be followed for survival until the end of the study. The schedule of study procedures for patients in long-term follow up is presented in Table 12 in Section 9.3 Study timetable and end of study.

5. STUDY ASSESSMENTS

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

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

5.1 Efficacy assessments

This study will evaluate the primary endpoint of OS. Secondary objective efficacy assessments of PFS, proportion of patients alive and progression free at 6 and 12 months from randomization (APF6, APF12) and ORR will be derived (by AstraZeneca) from site Investigator assessment according to RECIST 1.1. OS18 will also be evaluated.

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

The RECIST 1.1 guidelines (Appendix E) 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 randomization, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify target (defined measurable) and non-target lesions, and each lesion (and any new lesion) is evaluated in subsequent, on-treatment follow-up images. This allows determination of follow-up target lesion response, non-target lesion response, and overall time-point tumor responses (CR, PR, SD, PD or NE).

Efficacy for all patients (all arms) will be assessed on images collected Q6W ±1 week for the first 12 weeks relative to the date of randomisation, and Q8W ± 1 week thereafter until confirmed objective disease progression or off-study. It is important to follow the assessment schedule as closely as possible [refer to the study plans in Table 2 (treatment period), and Table 3 (follow up)]. If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her next regularly scheduled imaging visit.

AstraZeneca requests that at least one subsequent scan is acquired (and sent to the AstraZeneca-appointed imaging Contract Research Organization) after each initial progression event for all patients, across all arms of the study, no earlier than 4 weeks after and no later than the next regularly scheduled imaging visit after the initial progression event.

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

Following objective disease progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the follow-up schedules of assessments (Table 3). In addition, all patients will be contacted in the week following data cut-off to confirm survival status.

5.1.1 Reading of scans

Although scan assessments will be performed by Investigators, all images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization for QC and storage in the event that central review is required. Management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.

5.1.2 Survival assessments

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

In addition, patients on treatment or in survival follow-up will be contacted following the data cut-off for the primary analysis of PFS and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the data cutoff. Survival assessments may continue as per protocol (every 2 months) post the primary analysis of OS.

5.2 Safety assessments

5.2.1 Laboratory safety 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 (see Table 2 and Table 3).

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

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

The laboratory variables to be measured are presented in Table 4 (clinical chemistry), Table 5 (hematology), and Table 6 (urinalysis).

Other safety tests to be performed at Screening include assessment for hepatitis B surface antigen (HbsAg), hepatitis C antibodies, HIV antibodies.

Table 4 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH
Chloride[c]	T_3 free[d] (reflex)
Creatinine clearance[c]	T_4 free[d](reflex)
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyl transferase[c]	
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 one of these parameters is routinely measured, then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyl transferase, and magnesium, testing are to be performed at Screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated.

[d] Free T_3 or free T_4 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; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 5 Hematology

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

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at Baseline on Day 0 (unless all Screening laboratory hematology assessments are performed within 3 days prior to Day 0), and as clinically indicated.

[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 6 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix D for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 28 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IP (see Table 3).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 6.3.7.

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

5.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (Table 2 and Table 3). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at Screening only. Targeted physical examinations are to be utilized by the investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 6.3.6.

5.2.3 Electrocardiogram

Resting 12-lead ECGs will be recorded at Screening and as clinically indicated throughout the study (see Table 2). 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.

Situations in which ECG results should be reported as AEs are described in Section 6.3.7.

5.2.4 Vital signs

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

First infusion

On the first infusion day, BP and pulse rate will be collected/recorded in the eCRF prior to, during, and after infusion of each IO agent. BP and pulse rate will be collected prior to each infusion of EP therapy and as clinically indicated.

BP and pulse rate will be collected from patients in Arms 1 and 2 before, during, and after each infusion at the following times (based on a 60-minute infusion):

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

If the infusion takes longer than 60 minutes, then BP and pulse rate measurements should follow the principles as described above or be taken more frequently if clinically indicated. Additional monitoring with assessment of vital signs is at the discretion of the investigator per standard clinical practice or as clinically indicated.

Subsequent infusions

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

Situations in which vital signs results should be reported as AEs are described in Section 6.3.7. For any AEs of infusion reactions, please enter the vital signs values into the CRF.

5.2.5 Early Patient review for safety

Patients will be evaluated 7 days after the first dose of each cycle of chemotherapy across all arms to ensure early identification and management of toxicities.

We strongly recommend for any patient experiencing Grade 3-4 neutropenia that G-CSF is administered according to local practice.

5.2.6 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see Table 2 and Table 3) 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 changes from baseline or screening must be reported as an AE.

5.2.7 Other Safety Assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Toxicity Management Guidelines will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

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

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

5.3 Other assessments

5.3.1 Patient-reported outcomes

"PRO" is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PROs will be administered in this study: EORTC QLQ-C30 v3 (core questionnaire), EORTC QLQ-LC13 (lung cancer module), patient-reported outcomes version of the CTCAE (PRO-CTCAE), Patient's Global Impression of Change (PGIC), and the EuroQol 5-Dimension, 5-level health state utility index (EQ-5D-5L) (see Appendix F).

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

5.3.1.1 EORTC QLQ-C30

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

5.3.1.2 EORTC QLQ-LC13

For patients with SCLC, a disease-specific 13-item self-administered questionnaire for lung cancer was developed (EORTC QLQ-LC13; Appendix F) to be used in conjunction with the EORTC QLQ-C30 (Bergman et al 1994). It comprises both multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, hemoptysis, dyspnea, and pain) and side effects from conventional chemotherapy and radiotherapy (ie, hair loss, neuropathy, sore mouth, and dysphagia). Similar to the EORTC QLQ-C30, all questions except one have a 4-point scale: “not at all”, “a little”, “quite a bit” and “very much”. One question (no. 43, “Did you take any medicine for pain?”) has a response option of “yes” or “no”. The scoring approach for the EORTC QLQ-LC13 is similar to the EORTC QLQ-C30.

5.3.1.3 PRO-CTCAE

The PRO-CTCAE is included to address tolerability from the patients’ perspective. It was developed by the National Cancer Institute (NCI). The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Antonia et al 2014, Litwin et al 1998, Sprangers and Aaronson 1992). These symptoms have been converted to patient terms (eg, the CTCAE term “myalgia” has been converted to “aching muscles”). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. These items have been extensively evaluated by cancer patients to be clear, comprehensible, and measure the symptom of interest. In this study, only items that are considered relevant for the study, site of cancer, and cancer treatment are selected (see Appendix F).

5.3.1.4 Patients’ Global Impression of Change

The PGIC item is included to assess how a patient perceives his/her overall change in health status since the start of study treatment. Patients will choose from response options from “very much improved” to “very much worse.”

5.3.1.5 EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQol Group 2013).

Since 2009, the EuroQol Group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L) that expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability, and an improved ability to differentiate between different levels of health (Janssen et al 2008a, Janssen et al 2008b, Pickard et al 2007).

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state (see Appendix F).

5.3.2 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using an electronic tablet (ePRO) during clinic visits.

Each center must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per the schedule of assessments. The PRO questionnaires will be administered on the days specified in the schedules of assessments (see Table 2 and Table 3). The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.

It is important that the site staff carefully explain the significance and relevance of the data to participating patients so that they are motivated to comply with data collection. The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid biasing the patient's responses to the questions.
- PRO questionnaires must be completed in private by the patient.

- Patients should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is confidential. Therefore, if the patient has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device. The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items. The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.

A key aspect of study success is to have high PRO compliance. Therefore, it is essential to follow the schedule of assessments and that sites make sure the device is charged and fully functional at all times in order to minimize missing data.

5.3.3 Health care resource use

The assessment of health care resource use will increase the understanding regarding the relationship between treatment and tumor-related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction and bleeding. This will be captured and analyzed to inform submissions to payers.

To investigate the impact of treatment and disease on health care resource use, the following variables will be captured by hospital resource use module HOSPAD form:

- Planned and unplanned hospital attendances beyond study protocol mandated visits (including physician visits, emergency room visits, day cases, and admissions)
- Primary sign or symptom the patient presents with
- Length of hospital stay
- Length of any time spent in an intensive care unit

5.4 Pharmacokinetics

5.4.1 Collection of samples for pharmacokinetics analysis

Blood samples for determination of etoposide, carboplatin, cisplatin, durvalumab, and tremelimumab concentration in serum or plasma will be obtained according to the assessment schedules (see Table 2 and Table 3). Samples for etoposide, carboplatin, and cisplatin will be collected from selected sites only and will include approximately 6 patients per arm dosed with etoposide and carboplatin and approximately 6 patients per arm dosed with etoposide and cisplatin. AstraZeneca will inform the selected sites once this requirement has been fulfilled.

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

5.4.2 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to the assessment schedules (see Table 2 and Table 3).

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

5.4.2.1 Storage and destruction of pharmacokinetic/ADA samples

Durvalumab and tremelimumab PK and ADA samples will be disposed of a maximum of 10 years after the IPs are approved for marketing.

EP PK samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. PK and ADA samples may be disposed of or destroyed or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the clinical study report (CSR). Anonymised EP PK samples will be retained for no more than 5 years after the CSR is finalised.

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

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

5.5 Biomarkers

By participating in this study the patient consents to the collection and use of donated biological samples as described here. Tissue samples will be obtained from all screened patients where available. Based on availability of tissue, additional exploratory biomarkers may be evaluated as described in Section 5.5.1 Samples will be obtained according to the assessment schedules provided in Table 2 and Table 3.

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

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

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

5.5.1 Exploratory biomarkers

Blood and tumor samples for exploratory biomarker analyses will be obtained according to the schedules presented in Table 2. Details for collection, volumes, storage, and shipment of biologic samples are presented separately in the Laboratory Manual.

Baseline measures (and on-treatment changes) will be correlated with outcomes. Note that samples will be obtained from patients randomized to each treatment arm. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with Arms 1, 2, and 3.

The exploratory biomarker plan is described by sample type below.

Tumor mutational burden (TMB) and somatic mutations/alterations – tumor and plasma

SCLC is characterized by its high mutational load, as described in Section 1.1. Recent data from a Phase I/II study CheckMate 032 (A Phase I/II, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab in Subjects With Advanced or Metastatic Solid Tumors) have shown that patients with a high tumor burden (TMB high) derive greater clinical benefit from PD-1 blockade alone or in combination with CTLA-4 blockade. To better understand the significance of this finding and any impact this may have on patients in the present study (CASPIAN), we plan to assess tumor burden in both tumor and blood samples.

The overall mutation burden and/or somatic mutations/genomic alterations in tumor tissue and/or plasma may be assessed using methodologies including, but not limited to, whole exome sequencing to targeted sequencing. Such measurements may be correlated with response.

Tumor markers

This study will mandate the collection of archival/diagnostic tumor tissue, where available, which will be analyzed for various markers by immunohistochemistry.

A primary goal is to measure PD-L1, TMB, somatic mutations/genomic alterations and Delta-like canonical Notch ligand 3 (DLL3) expression to support exploratory objectives of investigating the following:

1. The relationship between a patient's PD-L1 expression and spatial distribution within the tumor microenvironment and efficacy outcomes with durvalumab, tremelimumab and EP.

2. The relationship between a patient's tumor mutational burden and/or presence of somatic mutations/genomic alterations and efficacy outcomes with durvalumab, tremelimumab and EP.

3. The impact, if any, of the level of DLL3 expression on efficacy outcomes with durvalumab, tremelimumab and EP (once a validated assay becomes available).

Other markers that may be assessed, subject to availability of tissue, include CD8 and CD4/FoxP3 protein expression in an effort to enumerate cytotoxic versus regulatory T cells. Based on availability of tissue, a panel of additional, immune-relevant markers expressed on TILs or on tumor cells may be assessed. Markers of special interest include, but are not limited to Ox40, GITR, PD-L2, Tim-3, CD137 and Lag 3.

Other tissue-based approaches may be pursued including RT-QPCR and in situ hybridization (eg, for detection of IFN-γ signaling genes such as *CXCL9*, *CXCL10*, *IFN-γ* itself, and *DLL3*), and/or somatic mutation detection methodologies.

Management of biomarker data

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

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

Summaries and analyses for exploratory biomarkers may be documented in a separate analysis plan and be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab or tremelimumab to generate hypotheses to be tested in future research.

Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed.

5.5.2 Labeling and shipment of biological samples

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

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

5.5.3 Chain of custody of biological samples

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

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

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

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

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

5.5.4 Withdrawal of informed consent for donated biological samples

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

The Principal Investigator will perform the following:

- ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed, or destroyed and the action is documented

- ensure that the organisation(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed or destroyed, the action is documented, and the signed document is returned to the study site

- ensure that the patient and AstraZeneca are informed about the sample disposal

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition 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, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 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

- Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement 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

For further guidance on the definition of an SAE, see Appendix A.

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.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

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

6.3.2 Follow-up of unresolved adverse events

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

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date when the AE started and stopped
- Maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Seriousness of criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 6.3.4
- Description of SAE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades,

the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but it is not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be an SAE if it satisfies the criteria shown in Section 6.2.

6.3.4 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."

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

6.3.5 Relationship to protocol procedures

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

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

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to record a list of signs and symptoms. However, if a diagnosis is known and there are other signs or

symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.7 Adverse events based on examinations and tests

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

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting investigator should use the clinical term 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 AEs.

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

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

6.3.8 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 D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

6.3.9 Disease progression

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

6.3.10 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 study treatment and have been identified after the patient's inclusion in this study.

6.3.11 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 treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study 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 in the eCRF. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca 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 after the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

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

For patients continuing to receive durvalumab treatment after final DCO and database lock, it is recommended that the patients continue the scheduled site visits according to Table 12 and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the Toxicity Management Guidelines. All data post the final DCO and database lock will be recorded in the patient notes only and not reported for the purposes of this study, with the exception of data collected in CRFs as per Table 12.

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

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs during the course of the study, then the investigator or other site personnel should inform 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 will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

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

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

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

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

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

6.5 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP 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 IP.

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

support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESIs/imAEs observed with durvalumab ± tremelimumab include the following:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis
- Hepatitis
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash/Dermatitis
- Nephritis/Blood creatinine increases
- Pancreatitis
- Myocarditis
- Myositis/Polymyositis
- Rare/less frequent imAEs including neuromuscular toxicities (eg, Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological ,rheumatological events, vasculitis, non-infections 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 and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in the Toxicity Management Guidelines (see Section 6.9). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines

apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

6.6 Overdose

6.6.1 Durvalumab or tremelimumab

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

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

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

6.6.2 Standard of Care

For patients randomized to the SoC (Arm3) group please refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE please record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

6.7 Pregnancy

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

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

6.7.1 Maternal exposure

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

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

If any pregnancy occurs during the course of the study, then the investigator or other site personnel should inform 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 will work with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab + EP combination therapy, 90 days after the last dose of durvalumab + EP, or 90 days after receipt of the final dose of durvalumab maintenance therapy, whichever is the longer time period.

Please follow the local prescribing information relating to contraception and the time limit for such precautions for EP agents.

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

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

6.8 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 (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- 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 an 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 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.9 Management of IP-related toxicities

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- 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 ± tremelimumab should be delayed.
- In the absence of a clear alternative etiology, all events should be considered potentially immune related and the Toxicity Management Guidelines should be followed.
- In the event that durvalumab ± tremelimumab is 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 across all arms in the study, if conditions allow.

If unsure how to manage a patient please contact the study physician at AstraZeneca to discuss individual cases. All toxicities will be graded according to NCI CTCAE, Version 4.03.

6.9.1 Durvalumab and durvalumab + tremelimumab

Comprehensive Toxicity Management Guidelines have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab [Medi4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these two compounds, these guidelines are applicable to the management of patients receiving either

drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and 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 Toxicity Management Guidelines 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 Toxicity Management Guidelines is provided to investigative site as an Annex document and is maintained within the Site Master File. In addition, a version of the current TMGs is available through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 3.9 of this protocol and Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting investigator.

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

The current Toxicity Management Guidelines is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

6.9.2 Standard-of-care agents

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. Communication with the Sponsor for questions is welcomed.

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 ± tremelimumab.

In the event that EP is delayed, durvalumab ± tremelimumab 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 across all arms in the study, if conditions allow.

6.10 Study governance and oversight

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

6.10.1 Safety Confirmation

An IDMC comprised of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab ± tremelimumab in combination with platinum based chemotherapy at two early stages of enrolment. A step wise approach will be adopted. The initial safety review will take place when the first 30 patients (10 in each arm) have completed the 1st cycle of treatment and had 21 days of follow up. A second review will take place when an additional 30 patients (10 in each arm) who have completed the 1st cycle of treatment and have had 21 days of follow up. At the time of the 2nd review, it is expected that the initial 30 patients would have had at least 6 weeks of follow up, with some patients receiving much longer. These two reviews will be carried out by the IDMC in an unblinded manner. After review, the IDMC will make a recommendation on whether the study should continue recruitment as planned, or hold recruitment. The IDMC recommendation will be communicated to all sites when available.

In addition, the IDMC will meet approximately every 6 months thereafter to continue safety monitoring.

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

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

AstraZeneca will supply durvalumab (MEDI4736) and tremelimumab, whereas the EP treatments will be supplied locally (Table 7).

Table 7 List of investigational products for this study

Investigational product	Dosage form and strength
Durvalumab (MEDI4736)	50 mg/mL, solution for infusion after dilution, IV
Tremelimumab	20 mg/mL, solution for infusion after dilution, IV
Etoposide and platinum-based chemotherapy	
Etoposide[a]	IV (as sourced locally)
Carboplatin[a]	IV (as sourced locally)
Cisplatin[a]	IV (as sourced locally)

[a] Under certain circumstances when local sourcing is not feasible, an etoposide and platinum-based chemotherapy treatment may be supplied centrally through AstraZeneca.
IV Intravenous.

7.1.1 Order of Administration

Arm 1:

Patients will receive 1 dose of tremelimumab (75mg) via IV infusion over 60 minutes, which will be followed by durvalumab (1500 mg) via IV infusion over 60 minutes.

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

If no issues are seen after tremelimumab is given during the first cycle, then at the investigator's discretion durvalumab can be given immediately after tremelimumab in subsequent cycles.

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.

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

Arm 2:

Patients will receive durvalumab (1500 mg) via IV infusion over 60 minutes.

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.

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

Arm 3:

Patients will receive carboplatin or cisplatin as an IV infusion over 60 minutes, followed by etoposide sequentially administered by a 60-minute IV infusion on Days 1, 2, and 3 of each cycle.

7.1.2 Durvalumab (MEDI4736)

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

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

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

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

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

A dose of 1500mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm 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.

7.1.3 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial concentrate solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% (w/v), polysorbate 80; it has a pH of 5.5. The nominal fill volume is 20.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary container until use to prevent excessive light exposure.

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab 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 tremelimumab 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.

A dose of 75 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 3.8 mL (ie, 75 mg of tremelimumab, with the dose volume rounded to the

nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If weight falls to ≤ 30 kg, weight-based dosing at 1 mg/kg will be a administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Standard infusion time is 60 minutes (± 5 minutes). 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. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

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

7.1.4 Standard of Care: EP

EP will either be locally sourced or centrally supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the Investigating site, including the sequence of drug administration. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, and will be labeled with local language translated text in accordance with regulatory guidelines.

7.2 Dose and treatment regimens

Patients will be randomized in a 1:1:1 ratio to receive treatment with durvalumab + tremelimumab + EP combination therapy, durvalumab (MEDI4736) + EP, or EP.

7.2.1 Treatment regimens

Durvalumab (MEDI4736) + tremelimumab combination therapy + standard-of-care therapy (Arm 1)

During Chemotherapy:

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 mins	4 doses Q3W Weeks 0, 3, 6 and 9
Tremelimumab	75 mg	IV	60 mins	4 doses Q3W Weeks 0, 3, 6 and 9
EP	Etoposide [80-100 mg/m^2] with either carboplatin [area under the curve 5-6] or cisplatin [75-80 mg/m^2]	IV	120 mins	4 doses Q3W Weeks 0, 3, 6 and 9

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing – equivalent to 20 mg/kg of durvalumab and 1mg/kg of tremelimumab Q3W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500mg and tremelimumab at 75mg.
EP Etoposide and platinum-based chemotherapy; IV Intravenous; Q3W Every 3 weeks.

Post-Chemotherapy:

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 mins	Q4W Week 12 to PD*
Tremelimumab	75 mg	IV	60 mins	1 dose at Week 16**

* Patients are treated until PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met
** In the case of dose delay(s) more than one durvalumab + tremelimumab combination dose can be given post chemotherapy to ensure that up to 5 combination doses are administered in Arm 1
Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing – equivalent to 20 mg/kg of durvalumab and 1mg/kg of tremelimumab q4w until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500mg and tremelimumab at 75mg.
IV Intravenous; Q4W Every 4 weeks.

Durvalumab (MEDI4736) + EP therapy (Arm 2)

During Chemotherapy

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 mins	4 doses Q3W Weeks 0, 3, 6 and 9
EP	Etoposide [80-100 mg/m^2] with either carboplatin [area under the curve 5-6] or cisplatin [75-80 mg/m^2]	IV	120 mins	4 doses Q3W Weeks 0, 3, 6 and 9

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 1500mg.

EP Etoposide and platinum-based chemotherapy; IV Intravenous; Q3W Every 3 weeks.

Post-Chemotherapy:

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 mins	Q4W Week 12 to PD*

* Patients are treated until PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg.

IV Intravenous; PD Progressive disease; Q4W Every 4 weeks.

EP therapy (Arm 3)

Agent	Dose	Route	Duration	Schedule
EP	Etoposide [80-100 mg/m^2] with either carboplatin [area under the curve 5-6] or cisplatin [75-80 mg/m^2]	IV	120 mins	4 doses[a] Q3W Weeks 0, 3, 6 and 9

[a] An additional 2 doses of EP (Weeks 12 and 15) can be given at the investigators' discretion if clinically indicated.

Prophylactic cranial irradiation (PCI) is permitted for patients in Arm 3 at the investigators' discretion if clinically indicated.

Patients who receive extra cycles of EP and PCI will still be expected to follow the planned scan schedule visits as detailed in Table 2 and Table 3.

EP Etoposide and platinum-based chemotherapy; IV Intravenous; Q3W Every 3 weeks.

The full dosing schema is provided below in Figure 5.

Figure 5 Dosing Scheme

Treatment arms	During Chemotherapy Q3W				Post Chemotherapy Q4W		
	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Week 12	Week 16	Week 20 to PD
Arm 1	EP + Durva + Treme	EP + Durva + Treme	EP + Durva + Treme	EP + Durva + Treme	Durva	Durva + Treme*	Durva
Arm 2	EP + Durva	EP + Durva	EP + Durva	EP + Durva	Durva	Durva	Durva
Arm 3	EP	EP	EP	EP**			

* In the case of dose delay(s) more than one durvalumab + tremelimumab combination dose can be given post chemotherapy to ensure that up to 5 combination doses are administered in Arm 1

** In Arm 3, EP can be given for an additional 2 cycles Q3W on Weeks 12 and 15 (ie, total 6 cycles post-randomization) if clinically indicated, at the investigators' discretion before patients enter Follow-up. PCI can also be given at investigators discretion. This does not alter the planned scan schedule Q8W starting at Week 12 for patients in Arm 3.

Durvalumab dose will be 1500 mg during chemotherapy and 1500 mg post-chemotherapy; tremelimumab dose will be 75 mg.

Note: Patients whose weight falls to 30 kg or below must receive weight-based dosing – equivalent to 20 mg/kg of durvalumab and 1mg/kg of tremelimumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500mg and tremelimumab at 75mg.

EP Etoposide and platinum-based chemotherapy; Durva Durvalumab; Treme Tremelimumab.

7.2.2 Duration of treatment and criteria for treatment through progression

Treatment with chemotherapy (EP) in Arms 1 and 2 will be limited to 4 cycles on a Q3W schedule subsequent to randomization. Patients in Arm 3 may receive an additional 2 cycles of EP (so 6 in total post-randomization), as clinically indicated, at the investigators' discretion.

Immunotherapy treatment, durvalumab ± tremelimumab, will be administered beginning on Day 1 (note: a window of up to 2 days is permitted between randomization and first dose of IP) until confirmed PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Patients in all arms with PD by RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment for as long as they are gaining clinical benefit. This also applies to EP; however, EP is restricted to a maximum of 4 cycles for patients in Arms 1 and 2 and a maximum of 6 cycles for patients in Arm 3.

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 ± tremelimumab.

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.

For patients randomized to Arm 3, crossover to durvalumab + tremelimumab or durvalumab monotherapy following confirmed disease progression will not be permitted.

Post final data cut-off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database lock may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database lock, it is recommended that the patients continue the scheduled site visits according to Table 12 and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to

manage AEs in accordance with the durvalumab toxicity management guidelines (please see Section 6.9.1).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database lock, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits assessment per its protocol. Any patient that would be proposed to move to such study would be given a new informed consent form.

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

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

7.4 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 IP label on the pack/bottle/carton for etoposide/carboplatin/cisplatin specifies the appropriate storage for these agents.

7.5 Compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the eCRF.

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

7.6 Accountability

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

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

drugs, and for appropriate destruction of study drugs. Certificates of delivery, destruction, and return should be signed.

7.7 Concomitant 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 period following the last dose of study drug. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

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

Restricted, prohibited, and permitted concomitant medications are described in Toxicity Management Guidelines.

For chemotherapy agents, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Table 8 Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
For all treatment arms	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [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

Prohibited medication/class of drug:	Usage:
For the durvalumab ± tremelimumab treatment arms only	
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 I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs. • Short-term premedication for patients receiving combination agents EP where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions. • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concurrently unless agreed by the sponsor

AE Adverse event; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; EGFR Epidermal growth factor receptor; EP Etoposide and platinum-based chemotherapy; 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 9 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
Herbal and natural remedies	Should be avoided during the study (with the exception of homeopathic remedies, which may be used following discussion with AstraZeneca)

7.7.1 Other concomitant treatment

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

7.7.2 Durvalumab drug-drug interactions

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

7.8 Post-study access to study treatment

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving durvalumab (MEDI4736) monotherapy up to confirmed progression (see Section 7.2.2).

8. STATISTICAL ANALYSES

8.1 Statistical considerations

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

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of the first randomized patient, and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data. The primary aim of the study is to compare the efficacy and safety of durvalumab + tremelimumab + EP with EP alone and the efficacy and safety of durvalumab + EP with EP alone.

Sections 8.2 to 8.5 describe the statistical analyses that apply to the global cohort data. For the China cohort, the same definitions of outcome measures (Section 8.4) and methods of statistical analyses (Section 8.5) will be applied unless specified otherwise in Section 8.6 or the supplementary China SAP. The same OS treatment effect under the alternative hypothesis is assumed in the plan for the China cohort analyses.

8.2 Sample size estimate

The study will randomize approximately 795 eligible patients 1:1:1 to durvalumab + tremelimumab + EP (Arm 1), durvalumab + EP (Arm 2), or EP (Arm 3). The randomization will be stratified based on planned platinum-based therapy in cycle 1 (carboplatin or cisplatin). Once global enrollment achieves 795 randomized patients, recruitment will continue in China only. A total of up to 189 patients from China will be randomized into the study (see Section 8.6 for details).

The primary objective of this study is to assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP (Arm 1 vs. 3) and the efficacy of durvalumab + EP treatment compared with EP (Arm 2 vs. 3) in terms of OS. To control for type 1 error, a significance level of 1% will be used for the analysis of Arm 1 vs. 3, and a significance level of 4% will be used for the analysis of Arm 2 vs. 3. The study will be considered positive (a success) if either of the OS analysis results are statistically significant. The sizing assumes a 3-month delay in separation of the OS and PFS curves between arm 1 vs. arm 3 and between arm 2 vs. arm 3, hence the use of average HRs.

There will be 2 data cut-off timepoints in the study. The interim analysis of OS will occur when approximately 318 OS events have occurred (60% maturity) in the durvalumab + tremelimumab + EP and EP treatment arms and approximately 318 OS events have occurred (60% maturity) in the durvalumab + EP and EP treatment arms. With a 15 month recruitment period in the global cohort and a minimum follow-up period of approximately 13 months, it is anticipated that this analysis will be performed approximately 28 months after the first patient is randomized).

The data cut-off for the primary analysis of OS will occur when approximately 425 OS events have occurred across the durvalumab + tremelimumab + EP and EP treatment arms (80%maturity) and approximately 425 OS events have occurred across the durvalumab + EP

and EP treatment arms (80% maturity). If the average true OS HR is 0.69, the study will have 89% power to demonstrate a statistically significant difference at the final analysis with a 2-sided 0.93% significance level (for an overall alpha of 1%) for the comparison of durvalumab + tremelimumab + EP versus EP (Arm 1 vs 3), and 96% power to demonstrate a statistically significant difference at a 2-sided 3.57% significance level (for an overall alpha of 4%) for the comparison of durvalumab + EP versus EP (Arm 2 vs 3); this translates to a 4.8-month benefit in median OS over EP (15.7 months vs 10.9 months).The smallest treatment difference that would be statistically significant is an average HR of 0.78 for durvalumab + tremelimumab + EP versus EP and 0.82 for durvalumab + EP versus EP. With a 15-month recruitment period and a minimum follow-up period of 27 months assumed, it is anticipated that this analysis will be performed 42 months after the first patient has been randomized.

A key secondary objective is to assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP (Arm 1 vs. 3) and the efficacy of durvalumab + EP treatment compared with EP (Arm 2 vs. 3) in terms of PFS. These analyses of PFS will be included in the MTP, as described in Section 8.5. If the average true PFS HR is 0.71, the study will have 90% power to demonstrate a statistically significant difference at the 5% level (using a 2-sided test) for the PFS comparisons when approximately 360 PFS events have been observed in the two treatment arms to be compared.

The secondary objective comparisons of durvalumab + tremelimumab + EP vs. durvalumab + EP for OS and PFS are not included in the MTP.

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 10.

Table 10 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
OS, PFS	Full analysis set (ITT population)
APF6, APF12, ORR, OS18, PROs, and symptom endpoints	Full analysis set (ITT population)
Demography	Full analysis set (ITT population)
PK data	PK analysis Set
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
Vital signs	Safety analysis set
ECGs	Safety analysis set

AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomization (ie, PFS at 12 months); APF6 Proportion of patients alive and progression free at 6 months from randomization (ie, PFS at 6 months); ECG Electrocardiogram; ITT Intent-to-treat population; ORR Objective response rate; OS Overall survival; OS18 Overall survival at 18 months after randomization; PFS Progression-free survival; PK Pharmacokinetic(s); PRO Patient-reported outcome.

8.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients. The FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment will be included in the analysis in the treatment arm to which they were randomized.

8.3.2 Safety analysis set

The safety analysis set will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized using the safety analysis set, according to treatment received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

8.3.3 PK analysis set

All patients who received at least 1 dose of IP per the protocol for whom any postdose data are available will be included in the PK analysis set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

8.4.1.1 RECIST 1.1-based endpoints

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 overall visit response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 21 days prior to randomization (unless the diagnostic scan is used as baseline, in which case this can be within 28 days prior to randomization – see Appendix E). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD).

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

8.4.1.2 Primary endpoints

The primary endpoints of this study are OS (Arm 1 vs. 3) and OS (Arm 2 vs. 3).

Overall survival

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of data cut-off for the analysis; if patients are confirmed to be alive or if the death date is after the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries.

8.4.1.3 Secondary endpoints

Progression-free survival

PFS (per RECIST 1.1 using Investigator assessments) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data, he or she will be censored at Day 1 unless the patient dies within 2 visits of Baseline.

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

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

- The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression.
- For investigational assessments, the date of progression will be determined based on the earliest RECIST 1.1 assessment/scan dates of the component that indicates progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Note: For target lesions, only the latest scan date is recorded in the RECIST 1.1 eCRF out of all scans performed at that assessment for the target lesions, and similarly for non-target

lesions, only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.

In the absence of significant clinical deterioration, the investigational site is advised to continue the patient on their randomized durvalumab + tremelimumab + EP or durvalumab + EP treatment until progression has been confirmed. If progression is not confirmed, the patient should continue their randomized durvalumab + tremelimumab + EP or durvalumab + EP treatment and on-treatment assessments. Treatment through PD in the EP arm is at the investigator's discretion; however, a follow up scan is required for all patients in the EP arm, even if a subsequent treatment is started.

Objective response rate

ORR (per RECIST 1.1 using Investigator assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR. The denominator is a subset of the ITT population who has measurable disease at Baseline. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

Proportion of patients alive and progression free at 6 and 12 months

The APF6 and APF12 will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed using site Investigator assessments) at 6 and 12 months, respectively.

Proportion of patients alive at 18 months

The OS18 will be defined as the Kaplan-Meier estimate of OS at 18 months.

8.4.1.4 Exploratory endpoints

Time from randomization to second progression (PFS2)

PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. The site will be asked whether the patient has had a second progression event on a regular basis (see Table 3) following the first progression event used for the primary variable PFS (the first progression) and the status recorded. Patients alive and for whom a second disease progression has not been observed will be censored at the last time known to be alive and without a second disease progression, that is, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

8.4.2 Calculation or derivation of safety variables

8.4.2.1 Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data.

"On treatment" will be defined as assessments between date of start dose and 90 days following discontinuation of IP (90 days after the last dose of durvalumab + tremelimumab combination therapy or durvalumab monotherapy or EP). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

AEs observed up until 90 days following discontinuation of study treatment (ie, 90 days after the last dose of durvalumab, tremelimumab, or EP) or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of AE summary tables. This will more accurately depict AEs attributable to study treatment only because a number of AEs up to 90 days following discontinuation of study treatment are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of study treatment (ie, without taking subsequent therapy into account).

Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of study treatment will be produced. These events will not be included in AE summaries.

8.4.2.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

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

$$QTcF = QT/RR^{\wedge}(1/3), \text{ where RR is in seconds}$$

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

$$\text{Corrected calcium (mmol/L)} = \text{Total calcium (mmol/L)} + ([40 - \text{albumin (G/L)}] \times 0.02)$$

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

For example:

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

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

8.4.3 Calculation or derivation of patient-reported outcome variables

PRO questionnaires will be assessed using the EORTC QLQ-C30 with the QLQ-LC13 module (HRQoL and lung cancer-specific symptoms), PRO-CTCAE, PGIC, and EQ-5D-5L. All items/questionnaires will be scored according to published scoring guidelines or the developer's guidelines if published guidelines are not available. All PRO analyses will be based on the FAS (intent-to-treat [ITT] population), unless stated. The PRO data will be assessed using mean/responder analyses based on published thresholds. Qualitative research with patients, clinicians and a review of the literature determine that the key symptoms and issues for patients are insomnia, appetite loss, dyspnea, hemoptysis, cough, chest pain, fatigue as well as physical functioning and global health status decline. These 7 symptoms have been identified as primary measures of interest. The physical functioning and overall health status domains of the EORTC QLQ-C30 are furthermore pre-specified endpoints of interest.

8.4.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 6 individual items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

8.4.3.2 Lung cancer module (EORTC QLQ-LC13)

The QLQ-LC13 is a lung cancer-specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms, treatment-related side effects, and pain medication.

8.4.3.3 Calculation or derivation of health state utility (EQ-5D-5L)

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents will select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied (Oemar et al 2013, Janssen et al 2008a, Janssen et al 2008b). In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

8.4.4 Calculation or derivation of pharmacokinetic variables

8.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modeling approach. The impact of physiologically relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between PK exposure and effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamic, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

8.4.4.2 Pharmacokinetic non-compartmental analysis

PK concentration data and summary statistics will be tabulated by time point. Peak and trough concentrations will be determined as data allow. Samples below the lower limit of quantification will be treated as missing in the analyses.

8.4.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab and tremelimumab. The immunogenicity titer and the presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

8.5 Methods for statistical analyses

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

- H0: No difference between durvalumab + tremelimumab + EP and EP

- H1: Difference between durvalumab + tremelimumab + EP and EP
- H0: No difference between durvalumab + EP and EP
- H1: Difference between durvalumab + EP and EP

The 2 primary endpoints are OS (Arm 1 vs. 3) and OS (Arm 2 vs. 3).The study has been sized to characterize the OS benefit of durvalumab + tremelimumab + EP versus EP and the OS benefit of durvalumab + EP versus EP.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized using the safety analysis set.

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

The following table (Table 11) details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note: all endpoints compare durvalumab + tremelimumab + EP versus EP and durvalumab + EP versus EP in all randomized patients (ITT population), unless otherwise indicated.

Table 11 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	Primary analysis using a stratified log-rank test for – durvalumab + tremelimumab + EP versus EP – durvalumab + EP versus EP Secondary analysis using a stratified log-rank test for: – durvalumab + tremelimumab + EP versus durvalumab + EP (ITT population) Sensitivity analysis using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank tests for: Secondary analysis using site Investigator tumour data (RECIST 1.1) for: – durvalumab + tremelimumab + EP versus EP (ITT population) – durvalumab + EP versus EP (ITT population) – durvalumab + tremelimumab + EP versus durvalumab + EP (ITT population) Sensitivity analyses using alternative censoring rules – attrition bias
Objective response rate	Logistic regression using Investigator data (RECIST 1.1)
Proportion of patients alive and progression free at 6 and 12 months	Kaplan-Meier estimates with 95% CI for progression-free survival at 6 and 12 months
Proportion of patients alive at 18 months	Kaplan-Meier estimates with 95% CI for overall survival at 18 months
Change from baseline in QLQ-C30 and QLQ-LC13 key symptom scores	Average change from baseline using a Mixed Model Repeated Measurements (MMRM) analysis
Time to symptom deterioration (EORTC QLQ-C30 v3 and LC13 endpoints)	Stratified log-rank test

EORTC European Organisation for Research and Treatment of Cancer; EP Etoposide and platinum-based chemotherapy; ITT Intent-to-treat; QLQ-C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1.

All outputs will be summarized by treatment arm for all randomized patients (ITT).

Multiple testing strategy

The multiple testing procedure (Figure 6) will define which significance levels should be applied to the interpretation of the raw p-values.

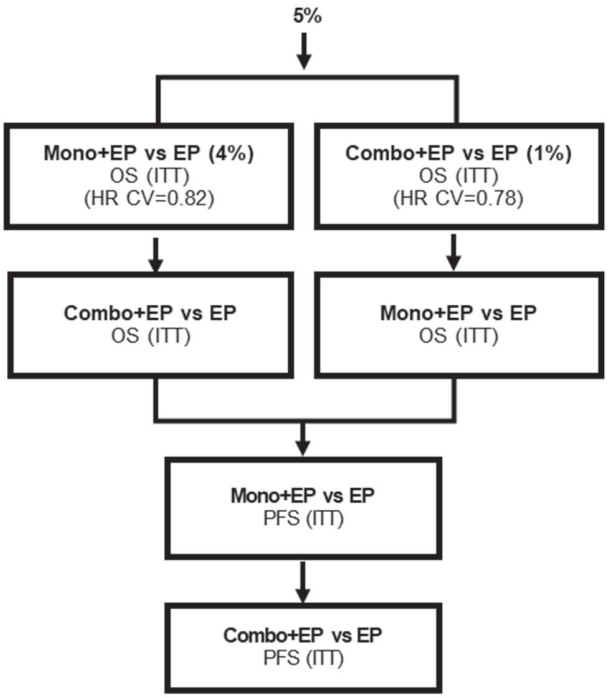
In order to strongly control the type I error at 5% 2-sided, a multiple testing procedure (MTP) with gatekeeping strategy will be used across the 2 primary endpoints of OS (Arm 1 vs. 3), OS (Arm 2 vs. 3) and the key secondary endpoint of PFS (Arm 1 vs. 3) and PFS (Arm 2 vs. 3). If the higher-level hypothesis in the MTP is rejected for superiority, the following hypothesis will then be tested as shown in Figure 6.

Hypotheses will be tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses will be tested in a pre-defined order as outlined in Figure 6. According to alpha (test mass) splitting and alpha recycling, the test mass that becomes available after each rejected hypothesis is recycled to secondary hypotheses not yet rejected

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

Figure 6 shows the multiple testing framework.

Figure 6 Multiple testing procedures for controlling the type 1 error rate



Note: Alpha recycling between Mono+EP vs EP and Combo+EP vs EP OS comparisons
Mono+EP vs EP = comparison of durvalumb+EP vs EP
Combo+EP vs EP = comparison of durvalumab + tremelimumab + EP vs EP

OS Overall survival; PFS Progression-free survival; EP Etoposide and platinum-based chemotherapy.

The testing procedure is hierarchical in that it starts with testing the 2 primary endpoints as outlined in Figure 6. The overall 5% type 1 error will be initially split between the 2 primary

endpoints: an alpha level of 4% will be allocated to the analysis of OS (Arm 2 vs. 3), and an alpha level of 1% will be allocated to the analysis of OS (Arm 1 vs. 3).

If the OS (Arm 2 vs. 3) analysis is significant, then 4% alpha will be recycled to the OS (Arm 1 vs. 3) endpoint;

If the OS (Arm 1 vs. 3) analysis is significant, then 1% alpha will be recycled to the OS (Arm 2 vs. 3) endpoint;

If both OS primary analyses are significant, then 5% alpha will be recycled to the PFS (Arm 2 vs. 3) endpoint. If PFS (Arm 2 vs. 3) is significant, then the 5% alpha will be recycled to PFS (Arm 1 vs. 3).

Spending alpha between the analyses in MTP in this way will strongly control type 1 error (Glimm et al 2009)

For the OS endpoint, there is 1 IA planned, and the alpha level will be controlled at the interim and primary analysis timepoints by using the Lan-DeMets (Lan and De Mets, 1983) spending function that approximates an O'Brien Fleming approach. The O'Brien Fleming boundaries for the OS interim and final analyses will be adjusted depending on the alpha used for the OS endpoint.

In addition, durvalumab + tremelimumab + EP will be compared with durvalumab + EP for OS and PFS. This comparison is not included in the MTP.

8.5.1 Analysis of the primary variable(s)

8.5.1.1 Overall survival

The primary analyses of the primary OS endpoints will occur when approximately 425 deaths have occurred across the durvalumab + tremelimumab + EP and EP treatment arms (80% maturity) and approximately 425 deaths have occurred across the durvalumab + EP and EP treatment arms (80% maturity). OS will be analyzed using a stratified log-rank test adjusting for planned platinum therapy in cycle 1 (carboplatin or cisplatin).

The effect of durvalumab + tremelimumab + EP versus EP treatment as well as durvalumab + EP versus EP treatment will be estimated by the HR together with its corresponding ([1-adjusted alpha] × 100%) CI and p-value for the ITT population.

The HR and CI can be estimated from the Cox proportional hazards model.

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

A secondary analysis of OS will be performed to compare durvalumab + tremelimumab + EP versus durvalumab + EP. These analyses will be performed using the same methodology as for the primary endpoints described above. The analysis to compare durvalumab + tremelimumab + EP versus durvalumab + EP will not be included in the multiple testing strategy.

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated.

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias, which is achieved by a Kaplan-Meier plot of time to censoring, where the censoring indicator of OS is reversed.

A subgroup analysis will be conducted comparing OS between durvalumab + tremelimumab + EP and durvalumab + EP versus EP in the following subgroups of the FAS: planned platinum therapy (carboplatin or cisplatin), age, gender, performance status, smoking status, AJCC stage (III/IV), CNS metastasis at baseline (Y/N), ethnicity, and geographical region.

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

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made, since all these analyses will be considered supportive of the analysis of OS.

For each subgroup level of a factor, the HR and 95% CI will be calculated from a Cox proportional hazards model that only contains a term for treatment. These HRs and associated two-sided 95% CIs will be summarised and presented on a forest plot, along with the results of the overall primary analysis.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and OS will not be formally analyzed. In this case, only descriptive summaries will be provided.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Progression-free survival

The analysis of the secondary PFS endpoint will be conducted using PFS programmatically derived from site Investigaror tumor assessments according to RECIST 1.1. The analysis will be performed in the ITT population using a stratified log-rank test adjusting for planned platinum therapy (carboplatin or cisplatin). The effects of durvalumab + EP versus EP treatment, and of durvalumab + tremelimumab + EP versus EP treatment, will be estimated by the HR together with corresponding 95% CIs and p-values.

A secondary analysis of PFS will be performed to compare durvalumab + tremelimumab + EP versus durvalumab + EP. This analysis will be performed using the same methodology as described above, but will not be included in the multiple testing strategy.

The assumption of proportionality will be assessed in the same way as for OS. The analysis will be based on the programmatically derived PFS using site Investigator assessments.

In addition, as a sensitivity analysis, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

Subgroup analyses and a forest plot will be provided for PFS comparing durvalumab ± tremelimumab + EP and EP alone in the same way as previously specified for OS.

No adjustment to the significance level for testing will be made since all these subgroup and sensitivity analyses will be considered supportive of the primary analysis of PFS.

8.5.2.2 Objective response rate

The ORR will be based on the programmatically derived RECIST using site Investigator data. The ORR will be compared between durvalumab + tremelimumab + EP versus EP as well as durvalumab + EP versus EP using logistic regression models. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). This analysis will be performed in the ITT population.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). Overall visit response data will be listed for all patients (ie, the FAS). For each treatment arm, best overall response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

8.5.2.3 Proportion of patients alive and progression free at 6 and 12 months

The APF6 and APF12 will be summarized (using the Kaplan-Meier curve) and presented by treatment arm along with confidence intervals using the log-log transformation.

This analysis will be performed in the ITT population.

8.5.2.4 Proportion of patients alive at 18 months (OS18)

The proportion of patients alive at 18 months (ie, OS18) will be summarized (using the Kaplan-Meier curve) and presented by treatment arm along with confidence intervals using the log-log transformation.

8.5.3 Patient-reported outcomes

For PRO symptoms and health related quality of life endpoints, the main concepts of interest have been identified using a literature review, and detailed qualitative interviews with SCLC patients and clinicians. The key symptoms were: cough, hemoptysis, dyspnea, chest pain, insomnia, fatigue and appetite loss. Therefore, these key SCLC symptoms will be identified as primary measures of interest. In addition, physical functioning and overall health status domains of the EORTC QLQ-C30 are furthermore pre-specified endpoints of interest.

8.5.3.1 Mixed-model repeated measures analysis

Change from baseline in cough, hemoptysis, dyspnea and chest pain as assessed by the EORTC QLQ - LC13 and insomnia, fatigue and appetite loss as assessed by the EORTC QLQ -C30 will be the primary analysis and assessment of PRO outcome measures. The analysis will be performed using a linear mixed model for repeated measures analysis of change from baseline in the scores for each assessment time point.

8.5.3.2 Time to deterioration

Time to symptom and function/HRQoL deterioration will be analyzed for each of the symptom scales/items, function scales, and global health status/QoL in EORTC QLQ-C30 and QLQ-LC13. This will be achieved by comparing between treatment groups using a stratified log-rank test as described for the primary analysis of OS. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

For each of the symptom scales/items, functional scales, and global health status/QoL, time to deterioration will be presented using a Kaplan-Meier plot. Summaries of the number and percentage of patients experiencing a clinically relevant deterioration or death and the median time to deterioration will also be provided for each treatment group.

Further details on how this data will be analysed and the threshold for a clinically relevant change will be detailed and pre-specified in the SAP.

8.5.3.3 EORTC QLQ-C30

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Details be will provided in the SAP.

8.5.3.4 EORTC QLQ-LC13

Summaries of original and change from baseline values of each symptom (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and other pain) and each treatment-related side effect (sore mouth, dysphagia, peripheral neuropathy, and alopecia) will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Details will be provided in the SAP.

8.5.3.5 PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the FAS. Further details will be provided in the SAP.

8.5.3.6 Patients' Global Impression of Change

PGIC data will be presented using summaries and descriptive statistics based on the FAS. Further details will be provided in the SAP.

8.5.3.7 EQ-5D-5L

Descriptive statistics, graphs, and listings will be reported for health state utility values and the visual analogue scale by visit as well as the change in these scores from baseline. To support future economic evaluations, additional appropriate analyses may be undertaken (eg, mean health state utility pre- and post-treatment and pre- and post-progression) and will be outlined in the payer analysis plan.

8.5.4 Health care resource use

The potential impact the disease and treatment have on health care resource use will be analyzed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies, and percentages) will be provided for each arm on the different types of hospital admissions, the length of stay of people admitted into hospital for at least 1 overnight stay, and length of stay of people admitted to intensive care/high dependency units, as well as the primary sign or symptom the patient presents with. To support submissions to payers, additional analyses may be undertaken, and these will be outlined in a separate payer analysis plan.

8.5.5 Safety data

Safety and tolerability data will be presented by treatment arm using the safety population.

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

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to durvalumab + tremelimumab combination

therapy, durvalumab monotherapy, and EP alone will be summarized. Time on study; durvalumab + tremelimumab, durvalumab, and EP dose delays/interruptions; and EP dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

8.5.6 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary will be provided for all evaluable patients in the PK analysis population.

8.5.7 Immunogenicity analysis

Immunogenicity results will be listed by patient, and a summary of the number and percentage of patients who develop detectable anti-durvalumab and anti-tremelimumab antibodies will be provided. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab and anti-tremelimumab antibodies.

The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated if data allow.

8.5.8 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or by using an appropriate data modeling approach.

8.5.9 Biomarker data

The relationship of DLL3, TMB, somatic alterations and PD-L1 expression and, if appropriate, other exploratory biomarkers to clinical outcomes (including but not restricted to PFS) may be presented based on sample availability. Summaries and analyses for exploratory biomarkers may be documented in a separate analysis plan and reported outside the CSR in a separate report.

8.5.10 OS interim analysis

One OS interim analysis is planned for durvalumab + tremelimumab + EP versus EP as well as for durvalumab + EP versus EP. This analysis will be performed by an IDMC. The interim analysis of OS will be conducted when approximately 318 OS events have occurred (60% maturity) in the durvalumab + tremelimumab + EP and EP treatment arms and approximately 318 OS events have occurred (60% maturity) in the durvalumab + EP and EP treatment arms. The Lan DeMets spending function that approximates an O'Brien Fleming approach will be used to account for the multiplicity introduced by including an interim analysis for superiority (Lan and DeMets 1983).

The criterion for superiority is a statistically significant improvement in OS at the interim analysis. If 75% of the OS events required at the time of the final OS analysis are available at the time of the interim analysis (ie, 318/425 OS events have occurred), the 2-sided significance level to be applied for the OS (Arm 2 vs 3) at the interim and final analysis would

be 1.43% and 3.57%, respectively and the 2-sided significance level to be applied for the OS (Arm 1 vs 3) at the interim and final analysis would be 0.23% and 0.93%, respectively.

If the OS interim analysis result does not meet the criterion of stopping for superiority, then all patients will continue to be followed for survival.

The recommendations from the IDMC will not reveal the results of the analyses but will take the form of "Continue/Modify/Recommend early submission/Stop." Details of the IDMC plan and communication process is provided in the IDMC Charter.

8.6 China cohort

The China cohort is defined as all patients from sites in China accredited by CFDA and enrolled into the study prior to the last patient last visit (LPLV) of the global cohort. The China cohort will include approximately 189 randomized patients. The global cohort consists of all patients randomized by the documented date of last patient randomized of the global cohort. Once global enrollment is complete, recruitment across all sites except for those from China will be closed, and the recruitment of patients in China will continue. Hence, a patient randomized in the China cohort prior to the last patient randomized in the global cohort will be included in both the global FAS and China FAS. A patient randomized in the China cohort after the last patient was randomized in the global cohort will be included only in the China FAS.

Per CFDA guidance, in addition to the evaluation of the global cohort data for primary, secondary, and safety objectives, evaluation of consistency in efficacy and safety in the Chinese and Asian populations is required to facilitate the benefit-risk assessment for Chinese patients. Thus, the efficacy and safety data in the China cohort will be summarized and analyzed separately where the same endpoint definitions (as described in Section 8.4) and the same methods for statistical analyses (as detailed in Section 8.5) are applied.

The China FAS will include all patients randomized in the China cohort and will be used for all China only efficacy analyses.

The China safety analysis set will consist of all patients randomized in the China cohort who receive at least one dose of study treatment.

Efficacy analyses for the China cohort will be performed when the OS data from the patients in this cohort are of similar maturity to those of the global cohort where significant clinical efficacy is established in the global cohort, eg, if OS efficacy is established at the primary analysis, a similar maturity to this will be used for the consistency evaluation.

All statistical analyses will be considered exploratory and only performed if sufficient numbers of events or patients are available (eg, ≥20 OS events) unless specified otherwise, descriptive statistics only will be presented. No adjustment for multiplicity will be made and

the procedure for hierarchical testing detailed in Section 8.5 will not be followed. OS efficacy evaluation for the China cohort will be performed once, respectively.

Details of the China cohort and Asian population analyses, including the vendor to perform the analyses, will be specified in the China supplementary SAP, which is to be finalized before the global cohort database locks for analyses.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is enrolled in the study, an AstraZeneca representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and train them in any study-specific procedures and IVRS/IWRS, WBDC, and any ePRO systems to be utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

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

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual, and study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure that withdrawal of informed consent for the use of the patient's biological samples is reported, biological samples are identified and disposed of or destroyed accordingly, and the action is documented and reported to the patient

The AstraZeneca representative will be available between visits if the investigators or other staff at the centers need information and advice about the study conduct.

9.2.1 Source data

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

9.2.2 Study agreements

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

9.2.3 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The investigator will be notified by AstraZeneca when recruitment is complete.

The end of the study is defined as “the last visit of the last patient undergoing the study.” The last patient in the global cohort was enrolled in Quarter 2, 2018. The estimated date of the last patient in the China cohort will be later than the estimated date of the last patient completed in the global cohort. The study is expected to end by Quarter 1, 2021.

Data collection during long-term follow up until study end:

After the primary analysis of OS is conducted, we will continue to follow ongoing patients in study for limited information (see Table 12).

Subjects continuing Durvalumab should be followed for below assessments Q4W (+/-1w). Subjects off-treament should be followed for below assessments Q8W (+/-1w). All SAEs experienced by patients whilst receiving treatment or within 90 days of treatment discontinuing must continue to be reported to the Sponsor within the usual timelines (ie, immediately, or no later than 24 hours of when the site become aware of the SAE).

Table 12. Schedule of study assessment and relevant eCRF pages to be completed during Long-term follow-up.

Assessment	Relevant eCRF page
Durvalumab Exposure (applicable only for patients continuing treatment post final analysis)	EX
Discontinuation (only for patients continuing Durvalumab treatment post final analysis)	DOSDISC
Survival assessment	SURVIVE
Statement of death	DEATH
Subsequent anti-cancer therapy	CAPRX1, CAPRXR2
Hospitalization and hospital resource utilisation	HOSPAD
All SAEs experienced by patients whilst receiving treatment or within 90 days of treatment discontinuing. If SAE is reported then all data relevant to the SAE (e.g. concomitant medications, laboratory data, dosing data, new medical or surgical history) should be submitted as part of the SAE report.	SAE
Performance Status	PSTAT

The study may be terminated at individual centers if the study procedures are not being performed according to GCP or if recruitment is slow. AstraZeneca may also terminate the

entire study prematurely if concerns for safety arise within this study or in any other study involving durvalumab and/or tremelimumab.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan.

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

AEs and medical/surgical history will be classified according to the terminology of the agreed version of MedDRA. Medications will be classified according to the WHO Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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

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

When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment-revealing data may be added thereafter, and the final database will be locked for the primary endpoint. Data collection per section 9.3 will continue post this lock for collection of limited data in long term survivors.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An EC/IRB should approve the final Clinical Study Protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

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

AstraZeneca will handle the distribution of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs/IRBs, and Principal Investigators safety updates or reports according to local requirements.

In line with local regulations, Principal Investigator may be responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

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

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant EC/IRB and, if applicable, also by the national regulatory authority, before implementation. Local requirements are to be followed for new version of the Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator. For distribution to EC/IRB, see Section 10.3.

If a change to Clinical Study Protocol requires a change to a center's ICF, AstraZeneca and the center's EC/IRB are to approve the revised ICF before the revised form is used.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and to determine if data

were recorded, analyzed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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Appendix A Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the 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).

Hospitalisation

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.

Important medical event or medical intervention

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

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

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

A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Genetic Research

RATIONALE AND OBJECTIVES

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies

GENETIC RESEARCH PLAN AND PROCEDURES

Selection of genetic research population

Study selection record

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

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and:**

Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

Previous allogeneic bone marrow transplant

Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main

study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 5.5.4 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients on Day 1 pre-dose (at or after randomization). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn on Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional, second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

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

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study, the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The

principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Patient data protection

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

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

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

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

INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Sections 5.2.1 and 6.3.8 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

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

Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TB ≥ 2xULN

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

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

Follow-up

Potential Hy's Law Criteria not met

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

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

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section 6.3.8)
- Notify the AstraZeneca representative who will then inform the central Study Team

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Actions Required for Repeat Episodes of Potential Hy's Law

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in

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

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

If Yes:

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

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section Potential Hy's Law Criteria Met of this Appendix

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

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

1. INTRODUCTION

This Appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for this study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiological progression.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Measurable:

A lesion, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have short axis[1] diameter of ≥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 diameter at baseline[2]).
- 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 (manual palpation) that is not measurable by CT or MRI.
- Previously irradiated lesions[3]
- Brain metastasis
- Skin lesions assessed by clinical examination

[1] The short axis is defined as the longest axis perpendicular to the long axis of the tumor.
[2] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).
[3] 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.

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 over cystic lesions as Target Lesions (TLs).

Target Lesions (TLs):

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 (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or multilobed organ (eg, lung) is each considered as a single organ.

Non-Target Lesions (NTLs):

Additional measurable lesions not recorded as TLs and non-measurable lesions (or sites of disease) should be identified as NTLs at baseline.

3. IMAGING MODALITIES

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

A summary of the methods of assessment (imaging modalities) to be used for RECIST 1.1 assessment of TLs, NTLs and new lesions, is provided in Table 13, (please see below).

Table 13 Summary of methods of assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray, Chest X-ray
	Chest X-ray	Bone scan
	Clinical examination	FDG-PET/CT
		Clinical examination
		Ultrasound

CT Computed tomography; FDG-PET/CT ^{18}FFluorodeoxyglucose positron emission tomography/CT; MRI Magnetic resonance imaging.

3.1 CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible images for measurement of TL, assessment of NTL, and identification of any new lesions.

It is recommended that IV contrast-enhanced CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement (eg, pelvis, brain) should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV MRI contrast of the abdomen is appropriate. In patients with severely compromised renal function a non-contrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, and scanner across all imaging time points per patient.

3.2 Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) 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 NTLs in patients that also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest X-ray

Chest X-ray assessment will not be used for assessment of TL. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 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.

3.4 Ultrasound

In this study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumor size. Ultrasound examination can, however, be used to identify the presence of new lesions. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

3.5 Endoscopy and laparoscopy

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

3.6 Tumor markers

Tumor markers on cytological or histological (biopsy) samples will not be used for tumor response assessments as per RECIST 1.1.

3.7 Histology and cytology

Histology on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to New Lesions or progression of NTLs, respectively.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as 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 may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan, however, a newly observed equivocal hot-spot on a bone scan which cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

3.9 FDG-PET/CT

^{18}F- Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F- Fluoro-deoxyglucose uptake[4] not present on baseline or prior 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 or prior 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 verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT

[4] A positive FDG-PET scan lesion should be reported only when uptake is greater than approximately twice that of the surrounding tissue or liver.

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 1.1 tumor assessments. Caution that 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.

4. TUMOR RESPONSE EVALUATION

4.1 Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including the entire liver and both 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 (eg, new lesions at follow up).

The baseline scan for this study must be done within 21 days prior to Day 1 of Cycle 1 and ideally should be performed as close as possible to the start of investigational product. The patient's diagnostic scan can be used as the baseline scan if it complies with recommended Image Acquisition Guidelines for assessing tumor burden in the chest and abdomen (including liver and adrenal glands) within 28 days prior to randomization.

Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks ± 1 week for the first 12 weeks (relative to the date of randomization; see Table 2 and Table 3 of the Clinical Study Protocol), then every 8 weeks ± 1 week thereafter until objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment/or subsequent therapy).

For patients who discontinue study drug due to toxicity in the absence of objective progression, objective tumor assessments should be continued every 6 weeks ± 1 week for 12 weeks (relative to the date of randomization) then every 8 weeks ± 1 week until confirmed objective disease progression.

Radiographic progression (PD by RECIST 1.1) requires collection of a the subsequent scan no earlier than 4 weeks after the prior assessment of PD and no later than the next regularly scheduled imaging visit. In patients receiving study treatment beyond the first RECIST 1.1-defined PD, if progression is not confirmed with the subsequent scan then the patient may continue on study treatment and continue with imaging assessments on their regular schedule.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at 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 objective disease progression for patients remaining on treatment, or until subsequent cancer therapy according to the clinical study protocol.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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 TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For 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 diameter.
- 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 TL has completely disappeared, the diameter should be recorded as 0 mm for the current and all subsequent scans. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.
- 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, and the overall visit assessment will be designated as PD.
- When a TL has had any intervention eg, definitive radiotherapy, embolization, surgery, etc., during the study, the size of the TL should still be provided where

possible and the intervention recorded in the RECIST case report form for that time-point and in all subsequent TL assessments (see 'Not evaluable' below). If a TL has been completely removed (surgery) or disappears following an intervention, the diameter should be recorded as 0 mm.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (Table 14).

Table 14 Evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter 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 decrease in sum of diameter 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 previous sum of diameters (nadir) - 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 from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. *Note:* if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

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

4.3 Non-target lesions

4.3.1 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 (Table 15).

Table 15 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. *Note:* for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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.

4.5 Symptomatic deterioration

Symptomatic (clinical) 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 radiologic evidence of disease progression at that time should continue to undergo tumor assessments where clinically feasible.

4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 16.

Table 16 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	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
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
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: Progressive disease, NE: Not evaluable, NA: Not applicable (relevant when no TLs or NTLs are present at baseline), NED: No Evidence of Disease (relevant when neither TLs nor NTLs are present at baseline).

5. CONFIRMATION OF RADIOLOGICAL PROGRESSION

A follow-up scan is collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD, and the Confirmation of Radiological Progression criteria described below are applied for tumor assessments of this follow-up scan. Patients with radiological PD who continue to receive study treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit.

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

- For patient management and treatment decisions

- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression.

Confirmation of Radiological Progression Criteria:

Confirmation of radiological progression guidelines are used to evaluate scans subsequent to a prior radiological PD. An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if any of the following criteria are met in a subsequent follow-up scan (acquired preferably at the next regularly scheduled imaging visit but no sooner than 4 weeks after RECIST 1.1-defined PD scan):

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, each with an absolute increase of at least 5 mm in sum of diameters compared to nadir (as per RECIST 1.1 definition)

- *and/or* significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint (as per RECIST 1.1 definition)

- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan time point compared with the immediate prior time point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point)

- *and/or* additional (brand) new unequivocal lesions at the follow-up scan time point (as per RECIST 1.1 definition).

NOTE: In order to have confirmed radiological progression, there should be two consecutive assessments meeting the PD definition, the first PD by RECIST 1.1 and the second PD using the confirmation of radiological progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, the patient may continue with assessments until the next PD by RECIST 1.1, which will also require a follow-up scan evaluated using the Confirmation of Radiological Progression criteria. **If the first PD (by RECIST 1.1) is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

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

6. CENTRAL REVIEW

All images will be collected, quality checked, and stored centrally by an Imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document.

7. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

If specified, all images will be collected, quality checked and stored centrally by the imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely upon the local assessments conducted by the Investigator.

7.1 CT Scan

CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomical region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

7.1.1 Anatomic coverage

Optimal anatomic coverage for most solid tumors is the chest and abdomen (and pelvis if indicated). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

7.1.2 Contrast administration

Optimal visualisation and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed then CT without IV contrast is an option for the thorax and abdomen (and pelvis examination). For brain imaging, MRI with IV contrast is the preferred method.

7.1.3 Slice thickness and reconstruction interval

It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

7.2 MRI SCAN

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies eg, neck) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

8. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Appendix F Patient Reported Outcomes: EORTC QLQ-C30, EORTC QLC-LC13, PRO-CTCAE, EQ-5D-5L, and PGIC

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Specimen

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen

ENGLISH

EORTC QLQ - LC13

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

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4
If yes, where _____				
43. Did you take any medicine for pain?				
1 No 2 Yes				
If yes, how much did it help?	1	2	3	4

SPECIMEN

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NCI- PRO-CTCAE ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⊗ in the one box that best describes your experiences over the past 7 days…

1. RASH	
Did you have any RASH?	
O Yes	O No

2. HAND-FOOT SYNDROME(A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS, OR PAIN)				
What was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3. ITCHY SKIN				
What was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4. ARM OR LEG SWELLING				
How OFTEN did you have ARM OR LEG SWELLING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

5. PAIN IN THE ABDOMEN (BELLY)				
How OFTEN did you have PAIN IN THE ABDOMEN (BELLY)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PAIN IN THE ABDOMEN (BELLY) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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NCI- PRO-CTCAE ITEMS

Item Library Version 1.0

Please think back over the past 7 days…

6. NUMBNESS OR TINGLING IN YOUR HANDS OR FEET				
What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7. DIZZINESS				
What was the SEVERITY of your DIZZINESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DIZZINESS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8. MOUTH AND THROAT SORES				
What was the SEVERITY of your MOUTH AND THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did MOUTH AND THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9. DRY MOUTH				
What was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

10. SHIVERING OR SHAKING CHILLS				
How OFTEN did you have SHIVERING OR SHAKING CHILLS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

11. PAIN, SWELLING, REDNESS AT A SITE OF DRUG INJECTION OR IV	
Did you HAVE ANY PAIN, SWELLING, REDNESS AT A SITE OF DRUG INJECTION OR IV?	
O Yes	O No

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EQ-5D-5L

Health Questionnaire

English version for the USA

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Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

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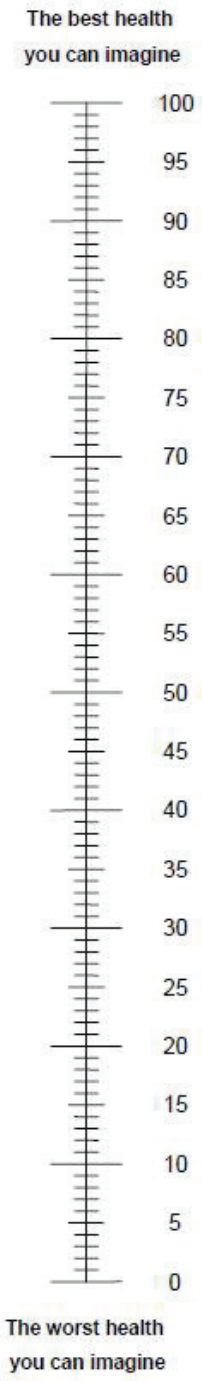
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the treatment I have received in this study, my overall health status is:

Please tick (✓) one box only:

- ☐ Very Much Improved
- ☐ Much Improved
- ☐ Minimally Improved
- ☐ No Change
- ☐ Minimally Worse
- ☐ Much Worse
- ☐ Very Much Worse

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English for USA

SIGNATURE PAGE

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