Clinical Study Protocol	
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A Phase IIIB Study in Untreated Patients with Extensive-Stage Small Cell Lung Cancer

A Phase IIIB, Single Arm Study, of Durvalumab in Combination with Platinum-Etoposide for Untreated Patients with Extensive-Stage Small Cell Lung Cancer reflecting Real World Clinical Practice in Spain (CANTABRICO)

Sponsor:

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VERSION HISTORY

Version 2.0, 25 September 2020
Section 6.4, table 6: Prohibited concomitant medications, has been updated with anti-epileptics, according to clarifications requested by AEMPS.
Version 3.0, 02 February 2021
Table 1 Schedule of assessments for durvalumab therapy treatment: New rows have been added in relation with the blood samples for biomarker analysis and for an optional tumor biopsy at progression disease. Minimun time between cycles has been clarified. **2.3.1.1 Durvalumab:** Safety information of durvalumab has been added due to the update of the investigational brochure of durvalumab. **Table 5 Study treatments:** Duration of etoposide, cisplatin and carboplatin infusion has been modified according to the summary of product characteristics. **5.1 Inclusion criteria:** Inclusion criteria 4b has been updated to allow the inclusion of patients with treated brain metastases treated with steroids and anti convulsants. **6.1.3. Order of Administration:** Duration of etoposide, cisplatin and carboplatin infusion has been modified according to the summary of product characteristics. **8.8 Biomarkers:** Information related with the additional blood samples and a tumor sample at progression disease have been added. **Table 11:** Information related with biomarkers has been added due to the addition of 2 new substudies (See appendix D and E). **Appendices J & K:** 2 new appendices has been added due to the addition of 2 new biomarkers substudies. **Appendix L:** Dosing Modification and Toxicity Management Guidelines for Durvalumab has been also added as anappendix.

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.

RESPONSIBLE PARTIES

Name	Professional title	Role in study	Affiliation	Email address
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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1. PROTOCOL SUMMARY

1.1Schedule of activities (SoA)

The procedures for the screening and treatment periods in this study are presented in Table 1 and Table 2, and the procedures for the follow-up period are presented in Table 2. Patients who continue beyond Cycle 13 will continue with all Cycle 13 assessments until termination of treatment (Table 1).

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

For durvalumab

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Dosing intervals of subsequent cycles (during chemotherapy interval is 21 days, post chemotherapy interval is 28 days) may be adapted +/-3 days as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and PRO assessments.

For EP treatment

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

Table 1 Schedule of assessments for durvalumab therapy treatment

		During Chemotherapy 1 cycle = 21 days				Post-Chemotherapy 1 cycle = 28 days		
	Screening	**C1**	**C2**	**C3**	**C4-C6**	**C5-C7 to PD**	**End of treatment**	
Week	**-4 to -1**	**0**	**Q3w ±3 days during chemotherapy and q4w ±3 days post-chemotherapy, unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1[a]**	**Q21days ±3 days during chemotherapy and q28days ±3 days post-chemotherapy, unless dosing needs to be held for toxicity reasons**					**For details, see Section**
Informed Consent								
Informed consent: study procedures[b]	X							5.1
Consent: sample for biomarker analysis (optional)	X							5.1
Study procedures								
Physical exam (full)	X							8.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	8.2.2
Vital signs[c]	X	X	X	X	X	X	X	8.2.3
ECG[d]	X	As clinically indicated						8.2.4
Concomitant medications	<----------						---------->	6.4
Demography, including baseline characteristics and tobacco use	X							5.1
Eligibility criteria	X							5.1, 5.2
Laboratory Assessments								
Clinical chemistry[e]	X	X[f]	X	X	X	X	X	Table 8
Hematology[e]	X	X[f]	X	X	X	X	X	Table 9
TSH[g], (reflex free T3 or free T4[h])	X	X	X	X	X	X	X	Table 8
Urinalysis	X	As clinically indicated						Table 10
Hepatitis B and C and HIV	X							8.2.1

		During Chemotherapy 1 cycle = 21 days				Post-Chemotherapy 1 cycle = 28 days		
	Screening	**C1**	**C2**	**C3**	**C4-C6**	**C5-C7 to PD**	**End of treatment**	
Week	**-4 to -1**	**0**	**Q3w ±3 days during chemotherapy and q4w ±3 days post-chemotherapy, unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1[a]**	**Q21days ±3 days during chemotherapy and q28days ±3 days post-chemotherapy, unless dosing needs to be held for toxicity reasons**					**For details, see Section**
Pregnancy test[i]	X	X	X	X	X	X	X	8.2.1
Monitoring								
WHO/ECOG performance status	X	X	X	X	X	X	X	8.2.6
AE/SAE assessment [k]	<----------						---------->	8.3
Patient follow up contact / Patient review for safety		Midway through Cycles 1, 2, and 3: days 14 of C1, 2, and 3						8.2.5
IP administration (Interval between 2 consecutive doses: 21 (+/-3) days during chemotherapy and 28 (+/-3) days after chemotherapy)								
Durvalumab [l]		X	X	X	X	X	X	6.1.1.1
Etoposide [n,o]		X	X	X	X			6.1.2.1
Carboplatin or cisplatin [n,p]		X	X	X	X			6.1.2.1
Other assessments and assays								
EORTC QLQ-C30 v3, EORTC QLQ-LC13 and PRO CTCAE [r,]		X	X	X	X	X	X	8.2.7
[redacted]	[redacted]					[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]		[redacted]	[redacted]		
[redacted] resource use[t]		X	X	X	X	X	X	8.2.8
Archival tumor biopsy (if available)	X							8.8
Fresh tumor biopsy (optional)							X (at PD)	

		During Chemotherapy 1 cycle = 21 days				Post-Chemotherapy 1 cycle = 28 days		
	Screening	**C1**	**C2**	**C3**	**C4-C6**	**C5-C7 to PD**	**End of treatment**	
Week	**-4 to -1**	**0**	**Q3w ±3 days during chemotherapy and q4w ±3 days post-chemotherapy, unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1[a]**	**Q21days ±3 days during chemotherapy and q28days ±3 days post-chemotherapy, unless dosing needs to be held for toxicity reasons**					**For details, see Section**
Efficacy evaluations								
Tumor assessments (RECIST 1.1)[q]	X	On-study tumor assessments will be performed following local standard practice, but at least with a maximun interval of 12 weeks. It is recommended that on-study tumor assessments occur q9w ± 1w for the first 12-18 weeks (relative to the C1D1, during chemotherapy treatment), and then, at least with a maximum interval of 12 weeks if signs or symptoms of progression do not happen before, if it is the standard procedure at study site, until RECIST 1.1-defined radiological progression plus an additional follow-up scan 4-8 weeks later.[g]						8.1, E

[a] Every effort should be made to minimize the time between inclusion and starting treatment (ie, within 1 day of inclusion).

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

[c] Body weight is recorded at each visit along with vital signs.

[d] Normal ECG basal mandatory (28 days maximum before first treatment). Other ECG will be performed under investigator criteria.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[f] 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.

[g] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

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

[i] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 3weeks during chemotherapy and every 4 weeks during durvalumab monotherapy. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion

[k] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed

[l] Results for LFTs, electrolytes, full blood count (during chemotherapy) and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[n] Durvalumab is infused first followed by the etoposide + cisplatin/carboplatin regimen

[o] Etoposide should be infused as local clinical practice, usually over 0.5 to 1 hour.

[p] Cisplatin and carboplatin should be infused as local clinical practice. If cisplatin, usually over 1 to 2 hours. If carboplatin, usually over 0.5 to 1 hour.

[q] See Section 6.1.3, Section 8.1, and E for additional details relevant to image acquisition, RECIST 1.1 assessments, and evaluation of scans after RECIST 1.1-defined progression.

[r] 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 QLQLC13 module.

[redacted]

[t] The site should complete the hospital resource use 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 hospital resource use form should continue to be completed until PD has been confirmed.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.
C Cycle; ECG Electrocardiogram; IM Intramuscular; LFT Liver function test; qXw Every X weeks; qXdays Every X days; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 2 Schedule of assessments for patients who have discontinued treatment with durvalumab + EP therapy

	Time since last dose of IP								
	Day (±3)	**Months (±1 week)**						**12 months and every 6 months (±2 weeks)**	**For details, see Section**
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**		
Physical examination (full)	X								8.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								8.2.3
Weight	X	X	X						8.2.3
Pregnancy test[a]	X	As clinically indicated							8.2.1
AE/SAE assessment	X	X	X						8.3
Concomitant medications	X	X	X						6.4
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy[b]								8.2.6
Subsequent anticancer therapy[c]	<----------								8.1
Survival status[f]		X	X	X	X	X	X	X (every 2 months)	8.1
Hematology	X	X	X						Table 9
Clinical chemistry	X	X	X						Table 8
TSH (reflex free T3 or free T4[g])	X	X	X						Table 8
Tumor assessment (RECIST 1.1)[i]	On-study tumor assessments will be performed following local standard practice, but at least with a maximun interval of 12 weeks, until RECIST 1.1-defined radiological progression plus an additional follow-up scan 4-8 weeks later.[g]								8.1

[a] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.
[b] WHO/ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.
[c] Details of any treatment for ES-SCLC (including surgery) post the last dose of IP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.
[f] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for ES-SCLC (including surgery) post the last dose of IP must be recorded in the eCRF.
[g] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[i] See Section 6.1.3, Section 8.1, and E for additional details relevant to image acquisition, RECIST 1.1 assessments, and evaluation of scans after RECIST 1.1-defined progression.

NA Not applicable; qXw Every X weeks; T3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

1.2Synopsis

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Protocol Title:

A Phase IIIB, Single Arm Study, of Durvalumab in Combination with Platinum-Etoposide for Untreated Patients with Extensive-Stage Small Cell Lung Cancer reflecting Real World Clinical Practice in Spain (CANTABRICO)

A Phase IIIB Study in Untreated Patients with Extensive-Stage Small Cell Lung Cancer

Rationale:

Recent data indicate that in 2018 lung cancer has been the leading cause of death from tumors in Spain (22,153 deaths). 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. Extensive-stage disease (ES) was defined as any tumor that extended beyond the boundaries of a single radiation port and is identified in ~70% of patients with SCLC.

Four to six cycles of platinum based chemotherapy, etoposide in combination with either cisplatin or carboplatin has been the standard care (SoC) for patients with ES SCLC for the past 25 years (Pignon et al 1992, Roth et al 1992). Despite high initial response rates of up to 70% (Rossi et al 2012), it is estimated that 80% of patients with limited stage and almost all patients with ES SCLC will relapse or experience disease progression (Clark and Ihde 1998). Therefore prognosis for patients with SCLC in general and particular ES SCLC is poor; the reported 2-year survival is only 5% and 5 years survival rate is less than 2% (Rossi et al 2012).

The phase III, randomised, open-label CASPIAN study showed a statistically significant improvement in overall survival (primary study endpoint) with first-line durvalumab and etoposide plus either cisplatin or carboplatin (platinum–etoposide) versus platinum–etoposide alone in patients with ES-SCLC at a planned interim analysis.

Despite the positive results, there remains limited information about the effectiveness and safety of durvalumab plus platinum-etoposide in ECOG PS 2 patients, as well as in patients having received CRT as a definitive treatment for a limited stage (LS)-SCLC and with progressive and platinum-sensitive disease at least 6 months after treatment; there is also limited information in patients with some stable comorbidities, controlled autoimmune diseases, or even in those patients where the investigator can expect benefit from a prophylactic cranial irradiation. Therefore, there remains an unmet need for additional data to help support and inform the health-care decisions in the use of durvalumab in combination with platinum–etoposide as first-line treatment for unselected patients with ES-SCLC in real clinical practice.

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on health-related quality of life (HRQoL) (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). In this study, the validated EORTC QLQ-C30 and EORTC QLQ-LC13 will be used to assess HRQoL, physical functioning, and symptom severity.

The present study will assess the safety and effectiveness of durvalumab plus platinum-etoposide in a real world ES-SCLC population until P&R approval of durvalumab in ES-SCLC based on CASPIAN results.

This trial will generate clinically relevant safety and efficacy data with durvalumab in combination with EP under conditions that reflect a real-world setting...

Objectives and Endpoints

Primary objective:	Endpoint/variable:
To describe safety profile of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC	Incidence of grade ≥ 3 AEs Incidence of imAE

Secondary objective:	Endpoint/variable:
To describe effectiveness of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.	Progression Free Survival (PFS). PFS rate at 6 months and at 1 year (PFS6, PFS12). Objetive Response Rate (ORR): using site investigator assessments according to RECIST 1.1. Duration of Response (DoR). DoR at 1 year (DoR12) Time to Treatment Discontinuation (TTD). Overal Survival (OS). The OS rate at 6, 12 and 18 months. *Time to event endpoints measured as time from first Durvalumab dose.*
To describe the impact of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC on patients' disease-related symptoms and Health Related Quality of Life (HRQoL) and (PROs).	Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration. Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30). Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life. Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13). Changes from baseline in PRO-CTCAE.
To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum–etoposide as first-line treatment.	- Number and length of hospitalizations - Number of visits to oncology service - Number of emergency visits - Number of outpatient visits - Number of imaging tests - Number of biopsy-related procedures - Treatment dose, duration, number of cycles

Objectives and Endpoints

Exploratory objective:	Endpoint/variable:
[redacted]	[redacted]

Overall design:

Phase IIIb, interventional, single arm, multicentre study to evaluate safety, effectiveness, use of resources and patient reporting outcomes in patients with ES-SCLC treated with durvalumab in combination with platinum–etoposide as first-line treatment in Spain.

Prophylactic cranial irradiation (PCI) is allowed in patients showing complete or partial responses after chemo-Durvalumab treatment under investigator criteria.

Study Period:

Estimated date of first patient enrolled: Q4 2020

Estimated date of last patient enrolled*: Q2 2021

Estimated date of last patient completed: Q2 2022

**Recruitment duration may be reduced or extended, until P&R approval of durvalumab in ES-SCLC based on CASPIAN results.*

Number of patients:

This is a safety study, and given the real-world setting, there is no formal predefined statistical hypothesis and no formal sample size calculation will be done.

A convenience sample size of approximately 85 patients was estimated based on the expected accrual potential during 6 months in 30 sites, although the recruitment duration may be reduced or extended, until P&R approval of durvalumab in Spain for ES-SCLC based on CASPIAN results, and the number of patients recruited could be higher. A maximum of 30% of recruited patients will have ECOG performance status of 2 at baseline.

Treatments and treatment duration:

Durvalumab will be concurrently administered with first-line chemotherapy (EP) on an every 3 week (q3w) schedule for 4 to 6 cycles, and will continue to be administered post-chemotherapy on an every 4 week (q4w) schedule until confirmed progressive disease (PD) or unacceptable toxicity.

Durvalumab + chemotherapy combination

- Durvalumab 1500 mg via IV infusion q3w concurrently with chemotherapy, starting on Week 0, for 4-6 cycles. Please note, if a patient's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab after consultation between the Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 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/m2] via IV infusion with either carboplatin [area under the curve (AUC) 5-6] via IV infusion or cisplatin [75 to 80 mg/m2] via IV infusion), starting on Week 0, for 4-6 cycles.

Durvalumab monotherapy

- Durvalumab 1500 mg via IV infusion q4w, starting 3 weeks after the last infusion of the combination, until confirmed progressive disease (PD) or unacceptable toxicity. Please note, if a patient's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients will continue therapy until clinical progression or confirmed radiological progression (defined in Appendix E).

Progression during treatment

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be 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 this scan is evaluated using the Confirmation of Radiological Progression criteria are outlined in Appendix E. If the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined PD which in turn will require a subsequent scan evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix E.

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 with tumor assessments until RECIST 1.1-defined PD plus an additional follow-up scan or until death (whichever comes first) and followed for survival.

Survival

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

Statistical methods

All statistical analyses will be performed by AstraZeneca or its representatives (e.g. CRO).

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of the first enrolled patient, and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data.

All analyses will be descriptive in nature. Categorical (e.g., gender) study measures will be reported using frequency and proportions and continuous measures (e.g., age) will be reported using mean, median, standard deviation and range. Additionally, Kaplan-Meier curves will be presented for time-to-event outcomes such as overall and progression free survival.

All analyses will be based on the intention to treat (ITT) population consisted of all enrolled patients who had received at least 1 dose of study drug (chemotherapy or Durvalumab). For the overall study population and for any subpopulation, estimated 95% CIs for various event rates will be calculated.

The incidence of common, or uncommon (<1%) serious adverse events will be estimated. Serious adverse events, grade 3/4 AEs, AE leading to death, AE leading to discontinuation, imAE and adverse events of special interest will be summarised by preferred term and incidence rates.

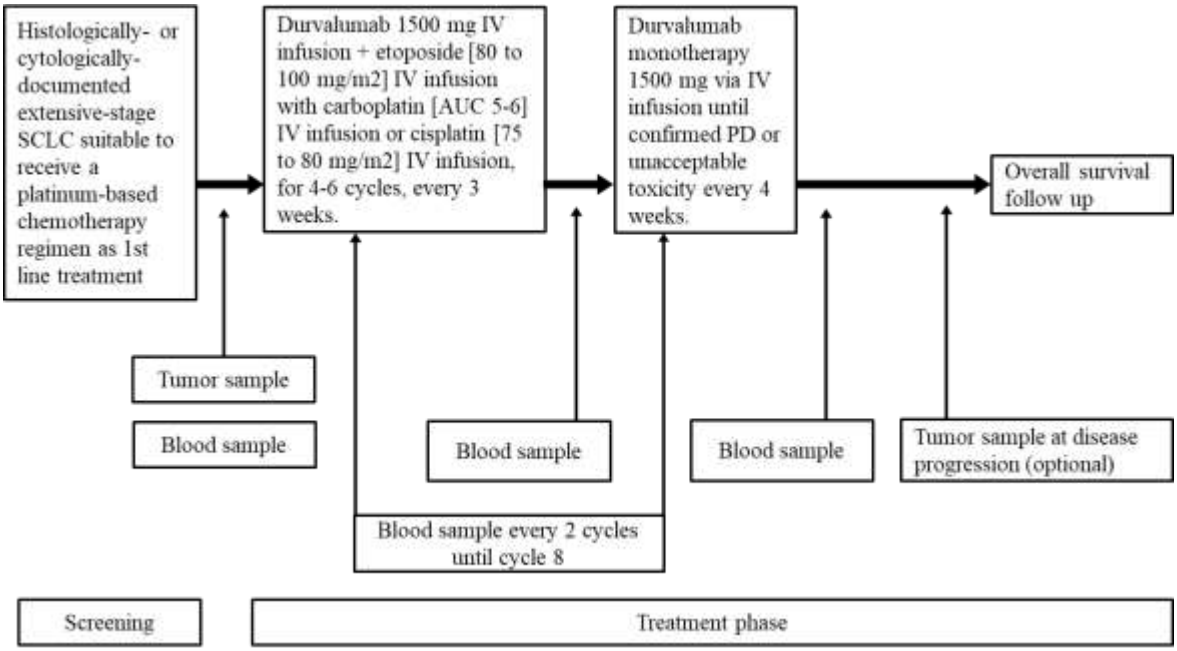
Baseline will be the last assessment of the variable under consideration prior to the intake of the first study drug (Durvalumab) dose.

Planned subgroup analyses of safety and effectiveness according to baseline characteristics include: ECOG status, gender, , presence of brain or liver metastases, smoking status, age of 65 years or older, and use of prophylactic cranial irradiation.

1.3Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



SCLC Small cell lung cancer; IV intravenous; AUC area under the curve; PD Progressive disease.

2. INTRODUCTION

Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018. According to population predictions, it is estimated that the number of deaths caused by tumors will increase to more than 16 million in the year 2040 (Ferlay et al 2012).

Also in Spain, cancer is one of the main causes of morbidity and mortality. The number of cancers diagnosed in Spain in 2020 is estimated to reach 277,394 cases according to REDECAN calculations, a number very similar to the year 2019.

Lung cancer will be the 4th tumor most frecuently diagnosed in Spain with 29,638 cases in 2020.

Recent data indicate that in 2018 lung cancer has continued to be the leading cause of death from tumors in Spain (22,153 deaths): 17,194 deaths in men, although it has experienced a 0.4% reduction compared to 2017; while in women 4,959 deaths were documented, which reflects an increase of 2.2% since 2017 (SEOM 2020).

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. Moreover, 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 also 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 stage was defined as tumor tissue that could be encompassed in a single radiation port, and extensive-stage disease (ES) was defined as any tumor that extended beyond the boundaries of a single radiation port. At present, limited stage is identified in ~30% of patients, and ES is identified in ~70% of patients.

Four to six cycles of platinum based chemotherapy, etoposide in combination with either cisplatin or carboplatin, without maintenance therapy has been the standard care (SoC) for patients with ES SCLC for the past 25 years (Pignon et al 1992, Roth et al 1992), and are recommended by major worldwide oncology treatment guidelines, ie, ASCO, NCCN, ESMO.

Despite high initial response rates of up to 70% (Rossi et al 2012), it is estimated that 80% of patients with limited stage and almost all patients with ES SCLC will relapse or experience disease progression (Clark and Ihde 1998). Therefore prognosis for patients with SCLC in general and particular ES SCLC is poor; the reported 2-year survival is only 5% and 5 years survival rate is less than 2% (Rossi et al 2012).

2.1Study rationale

The phase III, randomised, open-label CASPIAN study showed a statistically significant improvement in overall survival (primary study endpoint) with first-line durvalumab and etoposide plus either cisplatin or carboplatin (platinum–etoposide) versus platinum–etoposide alone in patients with ES-SCLC at a planned interim analysis. To our knowledge, this was the first phase 3 study with published data of anti-PD-1 or anti-PD-L1 in patients with ES-SCLC that permitted the use of investigator‘s choice of either cisplatin or carboplatin as the platinum component in platinum–etoposide and that allowed up to six cycles of platinum–etoposide (consistent with routine clinical practice) in the control group, compared with four cycles in the durvalumab plus platinum–etoposide group.

In CASPIAN, the addition of durvalumab to platinum–etoposide as first-line treatment for patients with ES-SCLC resulted in consistent and durable clinical benefit across overall survival, progression-free survival, and objective response, compared with a clinically relevant control group that is reflective of current global clinical practice for this challenging-to-treat disease. Our results align with those from the IMpower133 trial of atezolizumab plus carboplatin–etoposide, while providing significant progress in offering the flexibility of platinum choice in combination with immunotherapy, expanding treatment options for patients and physicians (Paz-Ares et al 2019).

In spite of the fact that the control arm in CASPIAN is quite close to real clinical practice, ES-SCLC patients have a rapidly progressive disease, symptomatic and some of them will be evaluated as PS 2 at diagnosis. We have quite limited information about the effectiveness and safety of durvalumab plus platinum-etoposide in this kind of patients, as well as in patients having received CRT as a definitive treatment for a limited stage (LS)-SCLC and with progressive and platinum-sensitive disease at least 6 months after treatment; there is also limited information in patients with some stable comorbidities, controlled autoimmune diseases, or even in those patients where the investigator can expect benefit from a prophylactic cranial irradiation. Therefore, there remains an unmet need for additional data to help support and inform the health-care decisions in the use of durvalumab in combination with platinum–etoposide as first-line treatment for unselected patients with ES-SCLC in real clinical practice.

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on health-related quality of life (HRQoL) (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for studies that use PFS as a relevant endpoint, where it is important to better understand in what regard the delay in disease progression is meaningful to patients. In this study, the validated EORTC QLQ-C30 and EORTC QLQ-LC13 will be used to assess HRQoL, physical functioning, and symptom severity.

The present study will assess the safety and effectiveness of durvalumab plus platinum-etoposide in a real world ES-SCLC population.

2.2Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the Investigator‘s Bochure.

2.2.1Immunotherapies

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

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

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

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of pre-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Hopwood et al 1995, Horn et al 2018, Hyde et al 1974, Iwai et al 2002, Paz-Ares et al 2019, Peifer et al 2012, Pignon et al 1992, Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

Pre-clinical data has now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and PD-L1 has promising clinical activity. Ipilimumab was first 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. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, small cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

2.2.2Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (SEOM 2020, Sprangers and Aaronson 1992, Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (SEOM 2020, Sprangers and Aaronson 1992, Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient‘s antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 8000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1.1 and Section 8.3.13. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

2.2.3Durvalumab in combination with chemotherapy

Nonclinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1) can have a positive effect on antitumor immunity. Patients with SCLC may be particularly susceptible to these immunotherapies given the high mutational burden of this disease (Salgia and Skarin 1998).

The use of combination chemotherapy is a mainstay of oncology therapy. The goal of combination chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus reducing the risk of developing resistance. Current investigations are now adding immunotherapeutics to chemotherapeutics to broaden antitumor responses.

Recently, several Phase III trials have been conducted to evaluate the combination of immunotherapy and chemotherapy in the treatment of ES-SCLC (NCT02763579, NCT03043872, NCT03066778). IMpower133 was a randomized, placebo-controlled phase III study that compared atezolizumab + etoposide/carboplatin (EC) with placebo + EC in the first line treatmet of ES-SCLC (Horn 2018). The study demonstrated a statistically significant improvement in OS with the combination of atezolizumab + EC compared to placebo + EC (Horn 2018). CASPIAN was a randomized, open label phase III trial that compared durvalumab, with or without tremelimumab, in combination with either cisplatin or carboplatin plus etoposide (EP) versus EP alone in treatment naïve patients with ES-SCLC. The CASPIAN trial demonstrated a statistically significant improvement in OS of durvalumab plus EP compared to

EP alone in first line treatment of ES SCLC (Paz-Ares 2019). Finally, KN604 was a randomized, placebo controlled phase III trial that compared pembrolizumab plus EP with placebo plus EP; while a numerical improvement in OS was observed, this did not reach statistical significance (Rudin 2020).

2.3Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of durvalumab may be found in the Investigator‘s Brochure.

2.3.1Potential benefits

2.3.1.1Durvalumab

More than 8000 patients have been treated across a large number of studies with durvalumab given as either a single agent or in combinations with a number of other anti-cancer therapies. The studies are being conducted across various tumour indications and stages of disease, including solid tumours and haematologic malignancies.

The majority of the safety and efficacy data currently available for durvalumab monotherapy are based on the first-in-human, single-agent study (Study CD-ON-MEDI4736-1108; hereafter referred to as Study 1108) in patients with advanced solid tumors, the study of durvalumab monotherapy in NSCLC (ATLANTIC Study [NCT02087432]), the study of durvalumab monotherapy in NSCLC following completion of platinum-based chemotherapy concurrent with radiation therapy (PACIFIC Study [NCT02125461]), and the study of durvalumab with or without tremelimumab as first line treatment for patients with advanced or metastatic NSCLC (MYSTIC Study [NCT02453282]). Details pertaining to these studies are provided in the current durvalumab IB.

2.3.1.2Durvalumab + chemotherapy

Studies evaluating agents targeting PD-L1 in combination with chemotherapy have yielded encouraging results.
CASPIAN is a randomised, open-label, multi-centre, global, Phase III trial in the first line treatment of 805 patients with ES-SCLC. The trial compared durvalumab in combination with etoposide and either carboplatin or cisplatin chemotherapy, or durvalumab and chemotherapy with the addition of a second immunotherapy, tremelimumab, versus chemotherapy alone. In the experimental arms, patients were treated with four cycles of chemotherapy. In comparison, the control arm allowed up to six cycles of chemotherapy and optional prophylactic cranial irradiation. The trial was conducted in more than 200 centres across 23 countries.

Durvalumab plus platinum–etoposide demonstrated a statistically significant and clinically meaningful improvement in overall survival versus platinum–etoposide alone, with an HR of 0.73 (95% CI 0.59–0.91; p=0.0047) (Paz-Ares 2019). Median overall survival was 13.0 months (95% CI 11.5–14.8) with durvalumab plus platinum– etoposide versus 10.3 months (9.3–11.2) with platinum– etoposide; the 12-month overall survival rates were 54% (47.4–59.5) versus 40% (33.7–45.8); and the 18-month overall survival rates were 34% (26.9–41.0) versus 25% (18.4–31.6). Overall survival benefit was observed across all clinically relevant patient subgroups. Consistent with the results for overall survival, progression-free survival (assessed without

formal statistical significance testing) was also in favour of durvalumab plus platinum–etoposide, as were objective response. Importantly, adding durvalumab to platinum-etoposide demonstrated significant and durable improvements in overall survival while maintaining quality of life, by delaying worsening of patient-reported symptoms, functioning, and HRQoL compared to platinum-etoposide alone.

Patients receiving durvalumab plus platinum–etoposide experienced reduced symptom burden over 12 months for pre-specified symptoms of fatigue, appetite loss, cough, dyspnea, and chest pain; a statistically significant difference over 12 months was observed for appetite loss in favor of durvalumab plus platinum–etoposide compared to platinum–etoposide alone. Patients in the durvalumab plus platinum–etoposide group experienced longer time to deterioration in a broad range of patient-reported symptoms, functioning and HRQoL compared to platinum–etoposide.

2.3.2Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or 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 normal 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 that 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 liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyper-thyroidism.

2.3.2.1Durvalumab

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

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

In monotherapy clinical studies, AEs at an incidence of $\geq$ 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, with the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.5).

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

2.3.2.2Durvalumab + chemotherapy

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

In the randomized phase III CASPIAN study, durvalumab + EP was well tolerated with a manageable safety profile as first line treatment for ES-SCLC. The safety profile was consistent with the known profile of all the agents and no new safety signals were identified (Paz-Ares 2019). In summary, regardless of causality, rates of AE of any grade (98.1% vs 97.0%), grade 3 or 4 AE (61.5% vs 62.4%), serious AEs (30.9% vs 36.1%), and those leading to discontinuation (9.4% vs 9.4%) were similar between durvalumab + EP vs EP alone. Adverse events of any cause leading to death occurred in 13 (5%) and 15 (6%) patients. The most common adverse events were haematological toxicities. Immune-mediated adverse events, defined as an event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate aetiology and the event required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy, were reported by 19.6% of patients treated with durvalumab + EP compared to 2.6% of patients treated with EP alone. The majority of immune-mediated AEs were low grade and thyroid related, consistent with the known safety profile of durvalumab.

External clinical data also supports these findings. In the randomized Phase III study IMpower133 demonstrated that the safety profile of atezolizumab combined with etoposide plus carboplatin was consistent with the previously reported safety profile of the individual agents, with no new findings observed (Horn 2018).

2.3.3Overall benefit/risk

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

Treatment with durvalumab 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.

Durvalumab + EP demonstrated a statistically significant and clinically meaningful improvement in OS versus EP alone in the phase III CASPIAN trial, reducing the risk of death by 27% for this challenging-to-treat disease. Consistent with the results for OS, PFS and ORR were also improved for durvalumab plus EP compared to EP alone. Importantly, these clinical benefits were observed in the context of a clinically relevant control arm that permitted up to 6 cycles of EP (compared with 4 cycles in the durvalumab + EP arm) and PCI at the investigator‘s discretion. The OS benefit was durable for durvalumab + EP compared with EP, as evidenced by the tail of the Kaplan-Meier curve; in the durvalumab + EP arm, an estimated 53.7% of patients were alive at 12 months and 33.9% of patients were alive at 18 months, compared to an estimated 39.8% and 24.7% of patients on the EP alone arm, respectively, at these landmarks. These gains in long term clinical benefit are meaningful to patients with this recalcitrant disease.

Durvalumab + EP was associated with a well-tolerated and manageable safety profile, consistent with the established safety profiles of each of the drugs to date. Regardless of causality, the rates of AEs of any grade, AEs of grade 3 or 4, SAEs, and AEs leading to discontinuation were similar between the arms. Collectively, these data suggest that the addition of durvalumab to EP did not increase the overall treatment burden of patients with ES SCLCover EP alone.

Taken together, the overall benefit/risk profile of durvalumab + EP remains favourable for continued development and supports the proposed study to further evaluate this combination for untreated patients with extensive-stage small cell lung cancer (SCLC) in a real-world setting.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary Objective:	**Endpoint/Variable:**
To describe safety profile of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC and also as monotherapy maintenance treatment.	Incidence of grade ≥ 3 AEs Incidence of imAE

Secondary Objective:	Endpoint/Variable:
To describe effectiveness of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.	Progression Free Survival (PFS). PFS rate at 6 months and at 1 year (PFS6, PFS12). Objetive Response Rate (ORR): using site investigator assessments according to RECIST 1.1. Duration of Response (DoR) DoR at 1 year (DoR12). Time to Treatment Discontinuation (TTD). Overal Survival (OS). The OS rate at 6, 12 and 18 months. *Time to event endpoints measured as time from first Durvalumab dose.*
To describe the impact of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC on patients' disease-related symptoms and Health Related Quality of Life (HRQoL) and (PROs).	Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30). Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life. Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13). Changes from baseline in PRO-CTCAE.
To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum–etoposide as first-line treatment.	- Number and length of hospitalizations - Number of visits to oncology service - Number of emergency visits - Number of outpatient visits - Number of imaging tests - Number of biopsy-related procedures - Treatment dose, duration, number of cycles

Secondary Objective:	Endpoint/Variable:
To describe effectiveness of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.	Progression Free Survival (PFS). PFS rate at 6 months and at 1 year (PFS6, PFS12). Objetive Response Rate (ORR): using site investigator assessments according to RECIST 1.1. Duration of Response (DoR) DoR at 1 year (DoR12). Time to Treatment Discontinuation (TTD). Overal Survival (OS). The OS rate at 6, 12 and 18 months. *Time to event endpoints measured as time from first Durvalumab dose.*
To describe the impact of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC on patients' disease-related symptoms and Health Related Quality of Life (HRQoL) and (PROs).	Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30). Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life. Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13). Changes from baseline in PRO-CTCAE.
To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum–etoposide as first-line treatment.	- Number and length of hospitalizations - Number of visits to oncology service - Number of emergency visits - Number of outpatient visits - Number of imaging tests - Number of biopsy-related procedures - Treatment dose, duration, number of cycles
Exploratory Objective:	**Endpoint/Variable:**

Secondary Objective:	Endpoint/Variable:
To describe effectiveness of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.	Progression Free Survival (PFS). PFS rate at 6 months and at 1 year (PFS6, PFS12). Objetive Response Rate (ORR): using site investigator assessments according to RECIST 1.1. Duration of Response (DoR) DoR at 1 year (DoR12). Time to Treatment Discontinuation (TTD). Overal Survival (OS). The OS rate at 6, 12 and 18 months. *Time to event endpoints measured as time from first Durvalumab dose.*
To describe the impact of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC on patients' disease-related symptoms and Health Related Quality of Life (HRQoL) and (PROs).	Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30). Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life. Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13). Changes from baseline in PRO-CTCAE.
To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum–etoposide as first-line treatment.	- Number and length of hospitalizations - Number of visits to oncology service - Number of emergency visits - Number of outpatient visits - Number of imaging tests - Number of biopsy-related procedures - Treatment dose, duration, number of cycles
[redacted]	[redacted]

Once the elegible participant has given the informed consent to be included at the program, study variables apart from those that will be used to assess the objectives, will include at least the following:

- **Demographic characteristics:** age, gender, race/ethnicity, smoking status, family history of cancer.

- **Clinical characteristics**: SCLC stage, tumor site and histology, number and location of metastases including brain metastases, presence of other primary malignancy at diagnosis, performance status according to the ECOG scale.

4. STUDY DESIGN

4.1Overall design

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

This is a Phase IIIb, interventional, single arm, multicentre study to evaluate safety, effectivenees, use of resources and patient reporting outcomes in patients with ES-SCLC treated with durvalumab in combination with platinum–etoposide as first-line treatment in Spain.

This study will include approximately 85 eligible patients at participating Spanish sites.

Durvalumab will be concurrently administered with first-line chemotherapy (EP) on an every 3 week (q3w) schedule for 4 to 6 cycles, and will continue to be administered as monotherapy post-chemotherapy on an every 4 week (q4w) schedule until confirmed progressive disease (PD) or unacceptable toxicity.

Prophylactic cranial irradiation (PCI) is allowed in patients showing complete or partial responses after the durvalumab + EP combination cycles, at the discretion of the investigator according to their local clinical practice.

Assessments will be conducted as indicated in Table 2 and Table 3.

Tumor assessments will be performed at Screening as baseline with follow-ups following local standard practice, but at least with a maximun interval of 12 weeks. It is recommended that on-study tumor assessments occur at Week 9 ±1 week from the date of inclusion for the first 12-18 weeks (during durvalumab + EP, relative to the C1D1), and then every 8 ±1 weeks until confirmed objective disease progression (please refer to Appendix E).

4.2Scientific rationale for study design

CASPIAN was a randomized, open-label, multi-centre, global, Phase III trial in the first line treatment of patients with ES-SCLC (NCT03043872). Durvalumab + EP demonstrated a statistically significant and clinically meaningful improvement in overall survival versus EP alone, with an HR of 0.73 (95% CI 0.59–0.91; p=0.0047). Overall survival benefit was observed across all clinically relevant patient subgroups.

The overall safety profile in CASPIAN was similar between the two groups, with similar frequencies of grade 3 or 4 adverse events, adverse events leading to discontinuation, and adverse events leading to death. The most common adverse events were haematological toxicities. Immune-mediated adverse events were mostly low grade and manageable with standard treatment guidelines and were numerically higher in the durvalumab plus platinum–etoposide group, and consistent with the known safety profile of durvalumab.

This phase IIIb single arm study, is supported by the available clinical safety and efficacy data provided by CASPIAN randomized, open-label, phase 3 trial compared to other currently available treatment options that offer a limited life expectancy. It is expected that durvalumab in combination with etoposide and either carboplatin or cisplatin chemotherapy followed by durvalumab monotherapy, will be approved by the EMA during 2020. This trial will provide an opportunity to further evaluate the safety profile and efficacy of durvalumab + EP in patient population that is reflective of real-world clinical practice, including patients with ECOG performance status 2 who have not been included in pivotal studies of immunotherapy in this disease setting.

4.3Justification for dose

4.3.1.1Durvalumab dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study 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 durvalumab IB).

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 AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median $C_{trough,ss}$ 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 serum 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 PK at the 20 mg/kg q4w regimen.

4.3.1.2Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data 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 to 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.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). 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 PK/pharmacodynamic 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 PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to 20 mg/kg q4w) is included in the current study.

4.3.1.3Rationale for durvalumab + EP dosing regimen

The dose and schedule of durvalumab proposed for this trial is consistent with that employed in the Phase III CASPIAN trial: a fixed dose of 1500 durvalumab Q3W while administered with chemotherapy followed by a fixed dose of 1500 mg durvalumab Q4W while administered as monotherapy maintenance until disease progression (Paz-Ares 2019). Likewise, the dose and schedule of etoposide and either carboplatin or cisplatin are consistent with those employed in the phase III CASPIAN trial as well as clinical practice guidelines (Paz-Ares 2019).

This trial will allow up to a maximum of 6 cycles of durvalumab + EP to be administered Q3W. While the CASPIAN trial allowed a maximum of 4 doses of durvalumab + EP, clinical practice guidelines have recommended between 4-6 doses of chemotherapy for treatment of ES SCLC (NCCN, ESMO). In the CASPIAN trial, 57% of patients in the control arm received 6 cycles of EP (Paz-Ares 2019), reflecting the importance of flexibility when determining the actual number of cycles of chemotherapy in clinical practice and the need to obtain safety data on the use of up to 6 cycles of durvalumab + EP. Therefore, this trial will allow up to 6 cycles of Durvalumab + EP.

4.4End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit.

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

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screening failures, refer to section 5.4.

In this protocol, ~~–~~enrolled" patients are defined as those who sign informed consent.
For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

2. Provision of signed and dated, written informed consent obtained from the patient/legal representative prior to performing any protocol-related procedures. The ICF process is described in Appendix A 3.

Age

3. Male or female ≥18 years at the time of screening.

Type of patient and disease characteristics

4. Patients must have histologically- or cytologically-documented extensive-stage SCLC (stage IV [T any, N any, M1a/b/c] or with T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan, according to American Joint Committee on Cancer Stage, 8th edition).

    a. Patients who had received chemoradiotherapy for LS-SCLC and have experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle, can be included under investigator criteria.

    b. Patients may be included if they either do not have brain metastases, or have brain metastases that are asymptomatic, or have brain metastases that have been treated at least 2 weeks prior to study treatment and are currently receiving 10 mg/day or less of prednisone or equivalent. Patients with suspected brain metastases at screening should have a CT/MRI of the brain prior to enrollment.

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

6. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 at enrolment/

a. Note: a maximun of 30% of total patients with PS2 will be allowed; once this limit is met, additional enrolled patients must have PS 0-1.

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

8. No prior exposure to immune-mediated therapy for cancer 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.

9. Adequate hematologic and organ function, defined by the following laboratory results obtained within 14 days prior to first Durvalumab dose:

   a. ANC ≥ 1500 cells/μL without granulocyte colony-stimulating factor support

   b. Platelet count ≥ 100,000/μL without transfusion

   c. Hemoglobin ≥ 9.0 g/dL

   d. INR or aPTT ≤ 1.5 × upper limit of normal (ULN); This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

   e. AST and ALT ≤ 2.5 × ULN, with the following exceptions: Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN; Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN.

   f. Serum bilirubin ≤ 1.5 × ULN; Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.

   g. 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):

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

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

10. 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. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of study treatment.For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures.

11. Life expectancy of at least 12 weeks.

Weight

12. Body weight >30 kg.

5.2 Exclusion criteria

1. History of allogeneic organ transplantation.

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

    a. Patients with vitiligo or alopecia

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

    c. Any chronic skin condition that does not require systemic therapy

    d. Patients with celiac disease controlled by diet alone

    Note: Patients without active disease in the last 5 years may be included but only after consultation with AstraZeneca.

3. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit

compliance with treatment requirements or compromise the ability of the patient to give written informed consent.

5. Malignancies other than SCLC within 3 years prior to screening if the patient has no evidence of disease, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent).

6. History of leptomeningeal carcinomatosis.

7. History of active primary immunodeficiency.

8. 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).

    a. NOTE: Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

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

10. Known allergy or hypersensitivity to Durvalumab (IMFINZI), etoposide, carboplatin, cisplatin, or any of their excipients.

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

Prior/concomitant therapy

12. Has received prior systemic treatment for ES-SCLC.

13. Planned consolidation chest radiation therapy.

14. Receipt of live attenuated vaccination within 30 days prior to the first dose of Durvalumab (IMFINZI). Note: Patients, if enrolled, should not receive live vaccine whilst receiving Durvalumab (IMFINZI) and up to 30 days after the last dose of Durvalumab (IMFINZI).

15. Major surgical procedure (as defined by the treating physician) within 28 days prior to the first dose of Durvalumab (IMFINZI). Note: Local surgery of isolated lesions for palliative intent is acceptable.

16. Prior exposure to any immune-mediated therapy, including, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including Durvalumab/(IMFINZI).

17. Current or prior use of immunosuppressive medication within 14 days before the first dose of Durvalumab (IMFINZI). The following are exceptions to this criterion:

    a. Intranasal, inhaled, topical steroids or local steroid injections

    b. Systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or its equivalent

    c. Systemic steroid administration required as premedication for hypersensitivity reactions (eg, CT scan premedication), or as premedication for chemotherapy is allowed.

Prior/concurrent clinical study experience

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

19. 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.

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

Other exclusions

21. Female patients who are pregnant or breast-feeding, or male or female patients of reproductive potential who are not willing to employ an effective method of birth control from screening to 90 days after the last dose of Durvalumab (IMFINZI).

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

5.3 Lifestyle restrictions

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

1. Female patient of child-bearing potential

    – Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 4) from the time of screening throughout the total duration of the drug treatment and the drug washout period 90 days after

the last dose of durvalumab. Non-sterilized male partners of a female patient of childbearing potential must use a male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

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

   – Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 4).

Please note, females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

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

- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 4. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 4 Highly effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method

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

4. Restrictions relating to concomitant medications are described in Section 6.4.

5.4Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be included. These patients should have the reason for study withdrawal recorded as ~~"e~~eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not included patients). Patients may be rescreened a single time.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAE).

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to platinum (carboplatin or cisplatin), etoposide and durvalumab.

6.1Treatments administered

6.1.1Investigational products

AstraZeneca will supply durvalumab (MEDI4736). SoC agents platinum (carboplatin or cisplatin) and etoposide will be supplied locally, as it is the standard treatment for these patients according usual clinical practice.

Table 5 Study treatments

	Durvalumab	***Etoposide***	***Cisplatin***	***Carboplatin***
Study treatment name:	Durvalumab (MEDI4736)	Etoposide	Cisplatin	Carboplatin
Dosage formulation:	500-mg vial solution for infusion after dilution, 50 mg/mL	Sourced locally by site	Sourced locally by site	Sourced locally by site
Route of administration	IV	IV	IV	IV
Dosing instructions:	Durvalumab 1500 mg via IV infusion over 60 minutes on Day 1 of each cycle.	Etoposide sequentially administered per local standards (usually over 30 to 60 minutes IV infusion) on Days 1, 2, and 3 of each cycle.	Cisplatin as an IV infusion per local standards (usually over 60 to 120 minutes on Day 1) of each cycle.	Carboplatin as an IV infusion per local standards (usually over 30 to 60 minutes on Day 1) of each cycle.
Packaging and labelling	500-mg vial solution for infusion after dilution.[b]	Sourced locally by site	Sourced locally by site	Sourced locally by site
Provider	AstraZeneca	Sourced locally by site	Sourced locally by site	Sourced locally by site

[a] Label text prepared for durvalumab (MEDI4736) will show the product name as ~~–M~~MEDI4736" or ~~–d~~urvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period. Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

6.1.1.1Durvalumab (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 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

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

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

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

A dose of 1500 mg (for patients >30 kg 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 15 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 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤30 kg, weight-based dosing at 20 mg/kg 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 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

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

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

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

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

6.1.1.2Etoposide + platinum

Etoposide + platinum (cisplatin or carboplatin) will be locally sourced and will be administered according to prescribing information or treatment guidance in general use by the Investigating site.

6.1.1.3Order of Administration

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.

Durvalumab infusion will then be followed by administration following local standards of an IV infusion of carboplatin usually over 30 to 60 minutes or cisplatin usually over 60 to 120 minutes , followed by etoposide sequentially administered usuallyover 30 to 60 minutes infusion on Day 1 of each combination cycle; etoposide will also be administered as an IV infusion on days 2 and 3 of each cycle up until a maximum of 6 cycles has been reached.

6.1.2Dose and treatment regimens

6.1.2.1Durvalumab (MEDI4736)

Patients will receive 1500 mg durvalumab via IV infusion q3w in combination with EP and q4w in monotherapy until clinical progression or RECIST 1.1-defined radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. (Please note, 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 q4w after consultation between Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w).

6.1.2.2Etoposide + platinum

Patients will receive, according to SoC, 4-6 cycles of:

- Etoposide: 80 to 100 mg/m2 daily on Days 1 to 3 (total dose 300 mg/m2) given q3w plus
- Carboplatin: AUC 5-6 on Day 1 given q3w, or
- Cisplatin: 75 to 80 mg/m2 intravenous (IV) on Day 1 given q3w

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. These agents are commonly used in ES-SCLC and will be given as per the product label for the indication and the NCCN and ESMO guidelines.

Prophylactic cranial irradiation (PCI) will be permitted; this will be at the investigators‘ discretion as per SoC guidance for ES-SCLC.

6.1.3Duration of treatment and criteria for treatment through progression and for retreatment

Durvalumab will be administered beginning on Day 1 until clinical progression or RECIST 1.1-defined radiological progression (refer to 0E), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1 -defined PD may continue to receive durvalumab at the discretion of the Investigator and patient as long as they are deemed to be receiving clinical benefit. A follow-up scan is to be collected after the initial RECIST 1.1 -defined PD, 4-8 weeks after the prior assessment of PD, and this follow-up scan is evaluated using the post-progression evaluation criteria outlined in 0E.

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, or spinal cord compression) will not be eligible for continuing durvalumab.

For all patients who are treated through progression, the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient may not have experienced a toxicity that required permanent discontinuation of study treatment.

- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status to >2

- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention

- The patient still fulfills the eligibility criteria for this study, with the execption of inclusion criterion 8

Patients who AstraZeneca and the Investigator determine may not continue treatment after RECIST 1.1-defined 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 with tumor assessments until RECIST 1.1-defined PD plus an additional follow-up scan or until death (whichever comes first) and followed for survival.

Post final data cut off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician considers they are gaining clinical benefit. Different drug supply options may be available and these will be proposed to the patient when the most appropriate alternatives for

continued treatment have been agreed between AZ and the Investigator. Options may incude participation in a new rollover study, or if durvalumab has been locally approved for use in this disease indication, patients may be discontinued from study treatment and transitioned to the marketed product, in accordance with local laws. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients‘ safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

6.1.4Storage

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), if needed, 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.

6.1.5Medical devices

Not applicable.

6.2Measures to minimize bias

6.2.1Patient enrollment

This is a single arm, open label study; no randomization or blinding will be performed.

If a patient withdraws from the study, then his/her enrolment code cannot be reused.

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

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

- Obtain signed informed consent before any study specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of inclusion.

- Obtain a unique enrollment number (E-code), through the Interactive Web Response System (IWRS). This number is the patient‘s unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

- Determine patient eligibility (see Sections 5.1 and 5.2)

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

Patients will begin treatment on Day 1. Treatment should start no more than 3 working days after being included. Patients must not be included and treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrollment code cannot be reused.

6.2.2 Procedures for handling incorrectly enrolled patients

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

Where a patient does not meet all the eligibility criteria but is included in error, or incorrectly started on treatment, the Investigator should inform the Study Medical Monitor immediately, and a discussion should occur between the Study Medical Monitor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Study Medical Monitor must ensure all decisions are appropriately documented and that the potential benefit:risk profile remains positive for the patient.

6.2.3 Methods for assigning treatment groups

Not applicable. This is a single arm study.

6.2.4 Methods for ensuring blinding

Not applicable. This is a single arm study.

6.3 Treatment compliance

Any change from the dosing schedule, dose delays/interruptions, dose reductions and dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP.

6.4 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the follow up period following the last dose of study drug.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, unit and frequency

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

Table 6 Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
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]) PCI is allowed in patients showing complete or partial responses after chemo-durvalumab treatment under investigator criteria.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP

Prohibited medication/class of drug:	Usage:
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).
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
Anti-epileptics	New treatment with phenytoin should not be started if patient is on treatment with cisplatin/carboplatin. If patient started taking phenytoin previously, monitor the levels of phenytoin in plasma while patient is on treatment with cisplatin/carboplatin and adjust the dose accordingly. There is a risk of exacerbation of convulsions due to the decrease of phenytoin digestive absorption and/or increased metabolism by the cytotoxic drug.

Table 7 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, 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

6.4.1 Background medication

6.4.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

6.4.3 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 metabolizing 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.

6.4.4 Rescue medication

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

6.5Dose modification

Dose delays are permitted for IO therapy (see Dosing Modification and Toxicity Management Guidelines). However, **dose reduction is not permitted**.

Chemotherapy dose modifications will be performed according SmPC guidelines.

6.6Treatment after the end of the study

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving durvalumab monotherapy up to the time that they discontinue the treatment for whatever reason (see Section 6.1.2).

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1Discontinuation of study treatment

An individual patient will not receive any further durvalumab or EP dose 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 (eg, for safety and survival follow up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) or as defined in the local prescribing information for the EP treatment.
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Clinical progression or confirmed radiological progression (refer to 0E) and Investigator determination that the patient is no longer benefiting from treatment with IP

- Completion of the study by the sponsor for obtaining the indication for ES-SCLC in combination with etoposide + platinum

7.1.1 Procedures for discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

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

Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed according usual clinical practice, at least q12w ±1w (relative to the date of inclusion), until RECIST 1.1-defined radiological PD plus an additional follow-up scan or death (whichever comes first) as defined the SoAs.

If a patient is discontinued for RECIST 1.1-defined progression, then the patient should have 1 additional follow-up scan performed 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.

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 the SoAs as an alternative.

7.2 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 4.4), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

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

- Lost to Follow up – site personnel should check hospital records, the patients‘ current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

7.3Withdrawal from the study

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 8.8.6)

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

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

The Investigator ensures the accuracy, completeness, for CRFs include: legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed paper/electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient‘s routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient over the duration of the study for the biomarker analysis will not exceed 90 mL. Blood samples for patient safety will be collected according ususal clinical practice at each study site.

Once the elegible participant has given the informed consent to be included at the program, the following demographyc and clinical variables will be collected:

- **Demographic characteristics:** age, gender, race/ethnicity, smoking status, family history of cancer.

- **Clinical characteristics**: SCLC stage, tumor site and histology, number and location of metastases including brain metastases, presence of other primary malignancy at diagnosis, performance status according to the ECOG scale.

8.1Efficacy assessments

This study will evaluate the efficacy of durvalumab + EP as secondary endpoints, in terms of OS, OS rates at 6, 12 and 18 months, as well as PFS, PFS rate at 6 and 12 months from inclusion, ORR, DoR, Time to Treatment Discontinuation and DCR, which will be derived (by AstraZeneca) using Investigator RECIST 1.1 assessments.

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

It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Treatment continues until clinical progression/deterioration or confirmed radiological progression (refer to 0E), and

scanning/tumor assessments continue throughout treatment until RECIST 1.1-defined radiological progression plus an additional follow-up scan (if clinically feasible).

The RECIST 1.1 guidelines (0E) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify Target Lesions (TLs) (defined as measurable) and Non-Target Lesions (NTLs). On-study images are evaluated for TLs and NTLs chosen at baseline, and for New Lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall timepoint responses (CR, PR, SD, PD, or Not Evaluable [NE]).

For all patients who are treated through progression, a follow-up scan is to be collected 4-8 weeks after the initial RECIST 1.1-defined PD; this follow-up scan is evaluated using the post-progression criteria outlined in 0E. If the subsequent scan confirms the immediate prior radiological PD, no additional scans are required unless the patients are allowed to continue study treatment; however, if the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined PD which in turn will require a subsequent scan evaluated using the post-progression criteria outlined in 0E.

8.1.1Central reading of scans

Not applicable.

8.1.2Survival 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 cutoff for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the data cutoff.

8.2Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs).

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. Pregnancy tests

may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

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

The laboratory variables to be measured are presented in Table 8 (clinical chemistry), Table 9 (hematology), and Table 10 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Table 8 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH[e]
Chloride[c]	T3 free[f] (reflex)
Creatinine[d]	T4 free[f] (reflex)
Gamma glutamyltransferase[c]	Urea or blood urea nitrogen, depending on local practice
Glucose	
Lactate dehydrogenase	

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

ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid-stimulating hormone.

Table 9 Hematology

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

Note: For coagulation parameters, activated partial thromboplastin time [either as a ratio or as an absolute value, in seconds]and international normalized ratio are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

[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 10 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

Note: Microscopy is preferred to investigate white blood cells, with use of high power field for red and white blood cells; dipstick can be used as well.

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to 0 for further instructions on cases of increases in liver biochemistry and evaluation of Hy‘s Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy‘s law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

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

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 8.3.7.

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

8.2.2Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.2.3Vital signs

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

First infusion

On the first durvalumab infusion, patients will be monitored and vital signs collected/recorded in eCRF prior to, during, and after infusion of IP as presented in the bulleted list below.

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

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [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)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab and EP.

Subsequent infusions

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

Situations in which vital signs results should be reported as AEs are described in Section 8.3.7. For any AEs of infusion reactions, the vital signs values should be entered into the CRF.

8.2.4Electrocardiograms

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

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

Situations in which ECG results should be reported as AEs are described in Section 8.3.7.

8.2.5Early patient review for safety

Not applicable.

8.2.6WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)

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

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

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

5. Dead

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

8.2.7Patient reported outcomes (PRO)

"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). (see Appendix H and, I).

The PRO instruments will be completed by the patients using a paper format questionnaire on day 1 of every cycle. All assessments should be completed without assistance from anyone according to the assessment schedules. It takes approximately 30 minutes for patients to complete the questionnaires; therefore, the burden to the patient is moderate.

8.2.7.1EORTC 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 H). 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).

8.2.7.2 EORTC QLQ-LC13

For patients with SCLC, a disease-specific 13-item self-administered questionnaire for lung cancer was developed (EORTC QLQ-LC13; Appendix I) 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: ~~–n~~ot at all", ~~–a~~ little", ~~–q~~uite a bit" and ~~–v~~ery much". One question (no. 43, ~~–D~~id you take any medicine for pain?") has a response option of ~~–y~~es" or ~~–n~~o". The scoring approach for the EORTC QLQ-LC13 is similar to the EORTC QLQ-C30.

8.2.7.3 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 ~~–m~~yalgia" has been converted to ~~–a~~ching 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.

8.2.7.4Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments in paper format 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. The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.

It is important that the significance and relevance of the data are explained carefully 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:

- 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 complete the questionnaires. 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.

8.2.8 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:

- Number and length of hospitalizations.
- Number of visits to oncology service.
- Number of emergency visits.
- Number of outpatient visits.
- Number of imaging tests.
- Number of biopsy-related procedures.
- Treatment name, dose, duration, number of cycles.

8.2.9Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) 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 Dosing Modification and 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
    - *(iv)* Any test to rule out an active infectious disease and any other causes should be performed under investigator criteria.

8.3Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3.

8.3.1Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2Time period and frequency for collecting AE and SAE information

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). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient‘s last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the Investigator should notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3Follow-up of AEs and SAEs

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

Any AEs that are unresolved at the patient‘s last AE assessment in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after the last dose of durvalumab), but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)

- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.5Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, 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 medication 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 B to the Clinical Study Protocol.

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

8.3.7 Adverse events based on examinations and tests

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

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see sections 8.3.9 and 8.310.

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to 0 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

8.3.9 Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of ES-SCLC or procedures to diagnose or treat ES-SCLC . Events which are unequivocally due to disease under

study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

8.3.10Disease progression

Disease progression can be considered as a worsening of a patient‘s condition attributable to the disease for which the investigational product 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, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.11New cancers

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

8.3.12Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF 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 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 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 Death page. If the death occurred as a result of an event that started post the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug then it should also be reported as an SAE.

8.3.13Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events

in order to characterize and understand them in association with the use of this investigational product.

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

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

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

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

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). 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.

8.3.14Safety data to be collected following the final DCO of the study

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient‘s safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4Safety reporting and medical management

8.4.1Reporting 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 in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one 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 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2Pregnancy

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

- If the pregnancy is discovered before the study patient has received any study drug

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

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

8.4.2.1Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day (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 provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.2.2Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab + EP combination therapy or 90 days after receipt of the final dose of durvalumab maintenance therapy.

Pregnancy of the patient‘s partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of durvalumab + EP combination therapy or 90 days after receipt of the final dose of durvalumab maintenance therapy 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 Ethics Committees (ECs) prior to use.

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 the SoAs).

8.4.3Overdose

8.4.3.1Durvalumab

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

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.3.2EP treatment

Use of etoposide or platinum in doses in excess of that specified in the protocol is considered to be an overdose. Please refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE please record the AE/SAE diagnosis or symptoms in the relevant AE modules of the eCRF.

8.4.4Medication error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.5Management 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.

- In the event that durvalumab is temporarily discontinued or delayed as part of the toxicity management guidance, EP should still be administered as scheduled; every effort should be made to ensure patients receive at least 4 cycles of EP in the study, if conditions allow.

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

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

8.4.5.1Specific toxicity management and dose modification information – Durvalumab

Comprehensive toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitor durvalumab [Medi4736] (PD-L1 inhibitor) Additionally, these guidelines are applicable when durvalumab 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 TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment (platinum and/or etoposide). The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines 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 should be

permanently discontinued (see Section 7.1 of this protocol and the Dosing Modification and Toxicity Management Guidelines). Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab by the reporting Investigator.

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

8.4.5.2Specific toxicity management and dose modification information – EP treatment

Chemotherapies are associated with a number of unwanted effects. Investigators should follow local standard clinical practice regarding dose modifications, including delays and reductions, for management of etoposide- and platinum-related toxicity. For specific information regarding the individual agent used in this study, please refer to 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).

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

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

8.5 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

The patient may give specific consent for sample collection for the biomarker analyses . The use of donated biological samples will be as described here (also see Table 11).

- Archival tissue samples will be obtained from all screened patients, if available (see Appendix J).

- Blood samples will be performed [redacted]
- Additional Blood samples will be performed [redacted]
- Fresh tissue sample will be obtained [redacted]

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

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

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

8.8.1Exploratory biomarkers

Blood and tumor samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoAs. Tissue samples will be collected from all screened patients in this study, if available, as specified in Section 8.8.1.1.

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

The exploratory biomarker plan is described by sample type below.

8.8.1.1Collection of tumor samples for exploratory tumor biomarkers

Tumor sample requirements:

• Provision of a tumor tissue [redacted] Refer to the Laboratory Manual for details.

At the screening visit, a tumor sample (formalin-fixed paraffin-embedded) will be obtained from all patients. The provision of tumor tissue sample is mandatory for the patients and requires a patient consent. If a tumor block exists and there is sufficient quantity to allow for biomarker analysis, then the tumor tissue block should be shipped to the central laboratory. If a tissue block is unavailable, unstained slides from the tissue block should be provided.

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

Tumor markers

Tissue obtained as part of screening procedures may be analyzed for potential biomarkers [redacted]

Other tissue-based approaches may be pursued including [redacted]

[redacted]

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

8.8.1.2Collection of samples [redacted]

Optional blood samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoAs (Table 1). Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

All samples collected for exploratory analyses will be stored at the site, a reference laboratory, or at AstraZeneca‘s facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.

The exploratory biomarker plan is described by sample type below.

[redacted]

[redacted]

Table 11: Biomarker analysis

Sample	Biomarker
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

8.8.2Management 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 and its appendices.

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.

8.8.3Storage, re-use and destruction of biomarker samples

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

8.8.4Labeling and shipment of biological samples

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

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

8.8.5Chain 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 receipt of arrival.

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, and auditing of external laboratory providers.

8.8.6Withdrawal of informed consent for donated biological samples

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

The Principal Investigator will:

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

8.9Medical Resource Utilization and Health Economics

For the purposes of economic evaluation, it is necessary to capture health care resource use related to the treatment and the underlying disease. Within the study, the following will be captured:

- Number and length of hospitalizations.
- Number of visits to oncology service.
- Number of emergency visits.
- Number of outpatient visits.
- Number of imaging tests.
- Number of biopsy-related procedures.
- Treatment name, dose, duration, number of cycles.

The above resource use data will mainly come from the patient‘s medical record and will be captured in the eCRF.

The assessment of health economic resource use data will provide important information for payers and will be used within economic evaluations of durvalumab.

Frequency and estimates of resource use, including length of stay and number of hospital admissions, will be derived from the health resource use information.

9. STATISTICAL CONSIDERATIONS

The primary aim of the study is to describe safety profile of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC and also as monotherapy maintenance treatment.

9.1Statistical hypotheses

There is no formal hypotheses in this study.

9.2Sample size determination

This is a safety study, and given the real-world setting, there is no formal predefined statistical hypothesis and no formal sample size calculation will be done.

A convenience sample size of approximately 85 patients was estimated based on the expected accrual potential during 6 months in 30 sites, although the recruitment duration may be reduced or extended, until P&R approval of durvalumab in Spain for ES-SCLC based on CASPIAN results. Therefore the number of patients recruited could be higher than 85 patients. A maximum of 30% of recruited patients will have ECOG performance status of 2 at baseline.

Assuming a sample size up to 85 and a 70% incidence of AE of CTCAE grade ≥3, the estimated precision will be no wider than 10% based on exact method (Clopper-Pearson). In addition, assuming a 20% incidence of imAE, the estimated precision will be no wider than 9% using the same method. An illustration of the precision around the varying incidences of AE for the pateints enrolled is provided in Table 12.

Table 11. Precision around varying incidence of AE

Precision of estimates of G3+ or imAE for varying Sample Sizes using Exact Binomial 95% CI				
Sample size	**True rate of Grade 3+ AE or imAE (%) and 95% CI**			
	20%	25%	60%	70%
85	**±9.0%** **12.1-30.1**	**± 9.7%** **16-35.3**	**10.9%** **48.8-70.5**	**± 10.0%** **59.7-80.0**

9.3 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 12.

Table 12 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy Data	
PFS, 6mPFS, 12mPFS	Safety analysis set
OS, 6mOS, 12mOS, 18mOS,	Safety analysis set
ORR, PROs, and symptom endpoints	Safety analysis set
DoR	Responders analysis set
TTD	Safety analysis set
PRO	Safety analysis set
Hospital resources	Safety analysis set
Demography	Safety analysis set
Biomarkers	Biomarkers Analysis Evaluable Set
Safety Data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
Vital Signs	Safety analysis set

AE Adverse event; XmPFS Proportion of patients alive and progression free at X months from inclusion; XmOS Proportion of patients alive X months from inclusion; ITT Intent-to-treat population; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; DoR Duration of Response; TTD Time to Treatment Duration; PRO Patient-reported outcome.

9.3.1 Safety analysis set

The safety analysis set will include all included patients that received at least one dose of study treatment. Safety, efficacy, and PROs data will be summarized using the safety analysis set. (Patients who were enrolled but did not subsequently go on to receive study treatment will not be included in the analysis.)

Responders Analysis Set: The subset of patients, within the Safety Analysis Set who are evaluable for response analysis and who achieve an objective response.

9.3.2 Biomarker analysis evaluable population

The Biomarker analysis set (BAS) will consist of all patients who received at least 1 dose of study treatment and for whom tumor and/or blood samples are available.

9.4 Outcome measures for analyses

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

AE: Number and proportion of patients with Grade 3 and Grade 4 AEs in total and by causality

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

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

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

AESI: Defined as an AE of scientific and medical interest specific to understanding of the IP. AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. In order to further characterize safety objectives related to AESIs, outcome measures will be assessed, which may include (and are not necessarily limited to) the following:

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

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

(c) Time from start of durvalumab to the onset of an AESI predefined type, all interventions of AESIs by type of intervention (including intervention with steroids, immunosuppressants, and/or hormone replacement therapy), and time from onset of an AESI type to resolution;

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

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

imAE: The imAEs will be assessed as a subset of AESIs. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate etiology.

PFS: Defined as the time from the first date of treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from IP or receives another anticancer therapy prior to progression.

PFS (days) = Date of event or Censor date – treatment start date +1

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1 unless he/she dies within 2 visits of baseline, in which case the date of death is the event date.

OS: Defined as the time from the first date of treatment until death due to any cause.

OS (days) = Death date or Censor date - treatment start date +1

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.

ORR: Based on Investigator−assessed response to treatment of CR and PR, per RECIST1.1.

DoR: Defined as the time from the date of first documented response per RECIST1.1 until the first date of documented progression per RECIST1.1 or death in the absence of disease progression.

DoR (days) = Date of PFS event or censoring – Date of first response +1

The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a patient does not progress following a response, then the patients‘ DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have a documented response.

Time to symptom deterioration (EORTC QLC-C30 and QLC-LC13): Defined as the time from start of study drug until the date of the first clinically meaningful symptom deterioration that is confirmed at the subsequent assessment or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study drug or receives another anticancer therapy prior to symptom deterioration.

Change from baseline (EORTC QLC-C30 and QLC-LC13, PRO-CTCAE): Defined as the post-treatment value minus the value at baseline. The % change from baseline will be calculated as (postbaseline value - baseline value) / baseline value x 100.

Treatment duration: Defined as Treatment end date - Treatment start date +1; will be summarized.

In addition, demographics, medical history, comorbidities, extent of disease at diagnosis (eg, stage and histology) will be reported. Specific details of planned analyses will be described in the SAP.

Use of resources: To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum–etoposide as first-line treatment. Description will include:

(a) Number of hospitalizations

(b) Length of hospitalizations: time from date of admission to discharge date

(c) Number of visits to oncology service

(d) Number of emergency visits

(e) Number of outpatient visits

(f) Number of imaging tests

(g) Number of biopsy-related procedures

(h) Treatment dose, duration, number of cycles

9.5Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalized within 3 months of the first enrolled patient and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations (n), mean, standard deviation, median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

For all summaries of AEs, only treatment-emergent AEs will be included. Treatment-emergent AEs are defined as events present at baseline that worsen in intensity after administration of IP or events absent at baseline that emerge after administration of IP, for the period extending to 90 days after the last dose of IP. Baseline will be the last assessment of the variable under consideration prior to the first IP dose administration.

9.5.1Analysis of the primary variables

Safety data will be summarized descriptively overall, by seriousness, by causality, and by maximum NCI CTCAE Grade. The exact 95% CIs around the incidence of Grade 3 and Grade 4 PRAEs will be reported.All outputs will be summarized for the safety analysis test.

A subgroup analysis may be conducted in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin or cisplatin), age, gender, performance status, smoking status and CNS metastasis at baseline (Y/N).

9.5.2Analysis of the secondary variables

9.5.2.1Safety variables

Adverse events
Total SAEs, AESIs, AEs leading to death, and AEs leading to study drug interruption or discontinuation will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term, causality, and maximum NCI CTCAE Grade. Deaths from all causes will be also summarized.

Data from all cycles of will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred term and CTCAE grade) will be listed individually by patient. Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP may be included in the AE summaries, but the majority of the AE summaries will omit the AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any AE that occurs after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

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 first IP dose administration.

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

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

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

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

The denominator used in laboratory summaries will include only 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 predose and at least 1 postdose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable, the patient need only have 1 postdose value recorded.

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

9.5.2.2Efficacy variables

Efficacy data will be reported for patients overall. Results of all statistical analysis will be presented using a 95% confidence interval (CI), unless otherwise stated.

The following table (Table 13) details which endpoints are to be subjected to statistical analysis.

Table 13 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Progression-free survival	Analysis by Kaplan Meier estimates using Investigator RECIST 1.1 assessments
Objective response rate	Analysis using Investigator RECIST 1.1 assessments
Duration of response	Analysis by Kaplan Meier estimates using Investigator RECIST 1.1 assessments, in patients with documented respnse
PFS at 6 and 12 months	Using the Kaplan Meier estimates of progression free survival at 6 and 12 months
Overall survival	Analysis by Kaplan Meier estimates
Overall survival at 6, 12 and 18 months	Using the Kaplan Meier estimates of OS at 6, 12 and 18 months
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Analysis by Kaplan Meier estimates. Change from baseline values will be calculated.

EORTC European Organisation for Research and Treatment of Cancer; 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.

Progression-free survival

The PFS analysis will be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments. The analysis will be performed using Kaplan Meier plots. Summaries of the number and percentage of patients experiencing a PFS event will be provided along with median PFS and its 95% confidence interval. In addition, the proportion of patients who are progression-free at 6 and 12 months will be presented.

A subgroup analysis may be conducted comparing PFS in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin or cisplatin), age, gender, performance status, smoking status and CNS metastasis at baseline (Y/N).

Other baseline variables may also be assessed if there is clinical justification. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

For each subgroup, the HR and 95% CI will be calculated by Cox regression and a log-rank test will be provided.

Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using the investigator tumor data. Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). 95% CI will also be presented.

Duration of response

DoR will be analyzed using the investigator tumor data in responding patients. Descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves.

Overall survival

OS will be analyzed using a Kaplan-Meier plots. 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 and corresponding 95% CI. In addition, the proportion of patients alive at 6, 12, and 18 months will be presented.

A subgroup analysis may be conducted comparing OS in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin or cisplatin), age, gender, performance status, smoking status and CNS metastasis at baseline (Y/N).

For each subgroup, the HR and 95% CI will be calculated by Cox regression and a log-rank test will be provided.

9.5.2.3Patient reported outcomes

Summary measures of visit and overall compliance and completion rates will be derived for each PRO questionnaire. Refer to the SAP for details.

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 SCLC patient and clinicians. The key symptoms were: cough, hemoptysis, dyspnea, chest pain, insomnia, fatigue and appetite loss.

Therefore we would like to pre-specify that an effective treatment would reduce time to deterioration and effect mean change from baseline in these key SCLC symptoms. The prespecified symptomatic endpoints are as follows: time to deterioration from baseline of cough, hemoptysis, dyspnea and chest pain from EORTC QLQ- LC13; and insomnia, fatigue and appetite loss from EORTC QLQ -C30; as well as average mean change of the key symptoms.

In addition, physical functioning and overall health status domains of the EORTC QLQ-C30 are furthermore pre-specified endpoints of interest.

The detail how this data will be analysed and the effect we would like to see to determine a symptomatic treatment effect will further be detailed and pre-specified in the SAP.

(a) EORTC QLQ-C30

If possible, time to symptom deterioration will be summarized for each of the 3 symptom scales (fatigue, pain, nausea/vomiting) and the 5 individual symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea).Similarly, a summary of QoL/function deterioration will be summarized for each of the function scales (physical, role, emotional, cognitive, and social) and global health status/QoL. This will be achieved by using Kaplan-Meier product limit methods to provide summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death, the median time to deterioration together with the corresponding 95% CIs, as well as the Kaplan-Meier plots.

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. Details will provided in the SAP.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥ 10 points for scales/items from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥ 10 points, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥ 10 points. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorised as improvement, no change, or deterioration as shown in Table 15.

Table 14. Mean change and visit response in health related quality of life

Score	Change from Baseline (points)	Visit Response
EORTC QLQ-C30 Global quality of life score	≥ +10	Improvement
	≤ −10	Deterioration
	Otherwise	No Change
EORTC QLQ-C30 symptom scales/items	≥ +10	Improvement
	≤ −10	Deterioration
	Otherwise	No Change
EORTC QLQ-C30 functional scales	≥ +10	Improvement
	≤ −10	Deterioration
	Otherwise	No Change

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire.

For each subscale, if < 50% of the subscale items are missing, then the subscale score will be divided by the number of nonmissing items and multiplied by the total number of items on the subscales (Fairman et al 2014). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Time to symptom deterioration

For each of the symptoms scales/items in the EORTC QLQ-C30 questionnaire, time to symptom deterioration will be defined as the time from start of study drug until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥ 10 points) that is confirmed at the subsequent assessment (at least 14 days apart) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study drug or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients with a single deterioration and no further assessments will be treated as deteriorated in the analysis. Patients whose symptoms (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO

assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1.

The analysis of time to symptom deterioration will be done with a subset of patients who have baseline scores of ≤90.

Time to quality of life/function deterioration
For QoL, time to deterioration will be defined as the time from start of study drug until the date of the first clinically meaningful deterioration (a decrease in the function scales or the global health status/QoL from baseline of ≥ 10 points) that is confirmed at the subsequent assessment (at least 14 days apart) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study drug or receives another anticancer therapy prior to QoL/function deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the QoL/function change could be evaluated.

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

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

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

(b) EORTC QLQ-LC13

Data will be summarized for each of the symptom items in EORTC QLQ-LC13 as outlined above for EORTC QLQ-C30.

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. Details will be provided in the SAP.

(c) **PRO-CTCAE**

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

9.5.2.4Healthcare resource use

An exploratory health economic analysis of hospital episodes including type of contact (hospitalization, outpatient, or day case), reason, length of stay by ward type (including intensive care unit), procedures, and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of durvalumab + EP. This would include providing descriptive statistics as appropriate, including means, median, and ranges. Costs associated with HCRU use will be quantified by multiplying the natural units of use of each resource by the cost of each resource retrieved from Spanish databases.

9.5.3Biomarker data

The relationship of exploratory biomarkers to clinical outcomes (including but not restricted to) of PFS, ORR, and OS will be explored.

Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.6Interim analyses

Not applicable

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11.SIGNATURES

ASTRAZENECA SIGNATURE(S)

Study Title: A Phase IIIB, Single Arm Study, of Durvalumab in Combination with Platinum-Etoposide for Untreated Patients with Extensive-Stage Small Cell Lung Cancer reflecting Real World Clinical Practice in Spain (CANTABRICO).

This Interventional Study Protocol has been subjected to an internal AstraZeneca review.
I agree to the terms of this Study protocol.

AstraZeneca representative

[redacted]

Date
(Day Month Year)

AstraZeneca representative

[redacted]

Date
(Day Month Year)

AstraZeneca representative

[redacted]

Date
(Day Month Year)

AstraZeneca representative

[redacted]

Date
(Day Month Year)

COORDINATING INVESTIGATOR

Study Title: A Phase IIIB, Single Arm Study, of Durvalumab in Combination with Platinum-Etoposide for Untreated Patients with Extensive-Stage Small Cell Lung Cancer reflecting Real World Clinical Practice in Spain (CANTABRICO).

I agree to the terms of this Study protocol.

I will carry out this study according to the procedures specified in this protocol and in accordance with the applicable local regulations.

Signature:

[redacted]

Date
(Day Month Year)

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the sponsor and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Regulatory Reporting Requirements for SAEs

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

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

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

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

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements local regulations and ICH guidelines, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient‘s legally authorized representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient‘s partner becomes pregnant during or within 90 days after the last dose of durvalumab, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been

analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law.

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

Each Investigator will ensure that all site personnel involved will respect the confidentiality of any information about trial subjects. Management of personal data from subjects participating in the trial, particularly as regards consent, will comply with General Data Protection Regulation (EU) 679/2016 and the Spanish Organic Law 3/2018 of 05th December on the protection of personal data.

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

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

A 6 Dissemination of clinical study data

A description of this clinical study will be available on *http://astrazenecaclinicaltrials.com* a*nd http://www.clinicaltrials.gov* as will the summary of the *main* study results when they are

available. The clinical study and/or summary of *main* study results may also be available on other websites according to the regulations of the countries in which the *main* study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator‘s site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A 10 Trial Monitoring and serious breaches

The clinical monitors are employees of APICES, and representatives of the sponsor. As such, they have the obligation to follow the trial closely so that all aspects of the trial are carefully monitored for compliance with applicable government regulations and with ICH E6(R2) guidelines.

The clinical monitors will visit the study sites and Investigators at intervals as defined in the monitoring plan, in addition to maintaining necessary contact through telephone, e-mail, and letter. The clinical monitors will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the study site Investigators and staff.

Serious breaches of the authorised protocol or of the Royal Decree 1090/2015 occurring in Spain must be reported by the sponsor without undue delay and no later than seven calendar days from becoming aware of the breach to the Spanish Agency of Medicines and Medical Devices (AEMPS) and the CEIm.

To this end, a serious breach shall be defined as a breach that may significantly affect the safety and rights of the trial subjects or the reliability and robustness of the data generated in the clinical trial.

Only serious breaches should be notified to the AEMPS and the CEIm, and the breaches that do not constitute a serious breach should not be notified.

Each study site Investigator must document and explain in the subject‘s source documentation any breaches from the approved protocol and / or the Royal Decree 1090/2015. Investigators may implement a breach to eliminate an immediate hazard to trial subjects without prior IEC informed consent approval, but the breach must be reported to the monitor/CRA within 1 working day. Such incidents will be evaluated for potential safety hazards of the ongoing study, and if deemed appropriate, a protocol amendment will be issued.

The monitor/CRA will document breaches throughout the course of monitoring visits.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent one of the outcomes listed above.
- Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the „Important Medical Event‘ criterion should be used. In certain situations, however, medical bjudgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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

B 3 Life threatening

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

B 4 Hospitalization

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

B 5 Important medical event or medical treatment

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

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

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

B 6 CTCAE grade

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels

into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A guide to interpreting the causality question

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

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

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

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

Causality of ‗related' is made if following a review of the relevant data, there is evidence for a ‗reasonable possibility' of a causal relationship for the individual case. The expression

‗reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

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

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

B 8 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

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

Medication error includes situations where an error.

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

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

- Drug name confusion
- Dispensing error (eg, medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the fridge when it should be at room temperature)
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

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

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

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

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps 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 AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

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

As collection of the biological sample(s) is an optional part of the study, then the patient may continue in the study.

The Investigator:

- Ensures patients‘ withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations 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.

C 3 International Airline Transportation Association (IATA) 6.2 guidance document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations 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 eg, 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 eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus 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 study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- **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 D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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 Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

D2. Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

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

D3. 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 subject who meets any of the following identification criteria in isolation or in combination:

ALT ≥ 3xULN
AST ≥ 3xULN
TBL ≥ 2xULN

Local laboratories being used:

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 subject meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
Promptly enter the laboratory data into the laboratory CRF

D4. Follow-up

1.1 Potential Hy's Law Criteria not met

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

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

1.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Appendix D, Section 6)

D5. 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.

As soon as possible 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, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. 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.

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

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

- Send updated 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 15 calendar days 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:

Provides any further update to the previously submitted SAE of Potential Hy‘s Law, (report term now _Hy‘s Law case‘) ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

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 still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D6. Actions Required When Potential Hy’s Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to subjects *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 subjects‘ 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 D, Section 3

D7. Actions Required for Repeat Episodes of Potential Hy’s Law

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

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

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

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease or did the subject meet PHL criteria prior to starting study treatment and at their first on-study treatment visit as described in section 6 of this Appendix

If **No**: follow the process described in Appendix D, Section 3 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the subject‘s condition[#] compared with when PHL criteria were previously met

If there is no significant change no action is required

If there is a significant change follow the process described in Appendix D, Section 3 for reporting PHL as an SAE

A ‗significant‘ change in the subject‘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.

D8 Laboratory tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry (issued July 2009) _Drug-induced liver injury: Premarketing clinical evaluation'

Appendix E Guidelines for evaluation of objective tumor response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this Appendix.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of Target Lesions (TLs), Non-Target Lesions (NTLs), and New Lesions (NLs) is provided in Table 15.

Table 15 Summary of imaging modalities for tumor assessment

Target Lesions	Non-Target Lesions	New Lesions
CT	CT	CT
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan (Scintigraphy)
		FDG-PET/CT

CT Computed tomography; FDG-PET/CT ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI Magnetic resonance imaging.

CT and MRI

Computed tomography (CT) with intravenous (IV) contrast is the preferred imaging modality (although magnetic resonance imaging [MRI] with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the Schedule of Activities [SoA; Table 1]), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every

attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; 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. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumor evaluation are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoA (table 1). Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis)
- IV contrast-enhanced CT or MRI of the head and neck
- IV contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when patients have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred)
2 Chest CT without IV-contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study
3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the patient has compromised renal function
4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT 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.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs 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 that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a progressive disease (PD) assessment at that time point.

FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or prior FDG-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the FDG-PET scan. The PET portion of the PET/CT introduces additional data that may bias an Investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

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

1 A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion 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.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other tumor assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Histology and cytology

Histology or tumor markers 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, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of complete response (all other disease disappears/reverts to normal) would be changed to partial response if an effusion remains present radiologically.

Measurability of tumor lesions at baseline

RECIST 1.1 measurable lesions at baseline:

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable lesions at baseline:

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural effusion, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- 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[3])
- Previously irradiated lesions[4]

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[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

[3] Lymph nodes with <10-mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

- Brain metastasis

Special considerations regarding lesion measurability at baseline:

- Bone lesions
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - 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 lesions thought to represent 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 TLs.

RECIST 1.1 TL selection at baseline:

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. TLs 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 that can be measured reproducibly should be selected.

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[4] Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

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 a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in whole (integer) millimeters and calculated values should be rounded to whole numbers. 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 assessment at baseline:

- For TLs 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.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.

RECIST 1.1 NTL selection at baseline:

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of tumor response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be

recorded in millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- 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. The choice of "Too large to measure" in the case report form will trigger an overall visit response of PD.
- When a TL has had an intervention, the following apply:
    - Target Lesion Intervention may include radiotherapy, embolization, excisional biopsy, surgery, etc. that is not a part of study treatment and might adversely affect the size of that Target lesion
    - If an Intervention on a Target Lesion is ticked in the case report form, the diameter of the lesion is still recorded (0mm if no longer present) and is included in the sum of diameters.
    - If a Target Lesion Intervention is ticked, the Intervention must be reported for all subsequent assessments of that Target lesion.
    - If a Target Lesion has an Intervention, the only Overall Visit Responses allowed to be recorded by the Investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
    - No visit with a recorded Target Lesion Intervention can be used as the minimum (nadir) sum of diameters.

Table 16 RECIST 1.1 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 the sum of diameters 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 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.
Not applicable (NA)	Only relevant if no TLs present at baseline.

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

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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.

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 unequivocal progression by NTLs. A modest ‗increase' in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease (SD) or progressive disease (PR) of target disease will therefore be extremely rare.

Table 17 RECIST 1.1 evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTLs.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 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 1 or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. 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.
Not applicable (NA)	Only relevant if no NTLs present at baseline

CR Complete response; NE Not evaluable; NTL Non-target lesion; PD Progression of disease; TL Target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the case report form. The presence of 1 or more NLs is assessed as progression. The finding of a NL 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 NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

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

RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 18.

Table 18 RECIST 1.1 overall visit response

Target Lesions	Non-Target Lesions	New Lesions	Overall visit 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 or NA	No	PR
SD	Non PD or NE or NA	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

[a] Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.

Note: An overall assessment of Complete Response (all other disease disappears/reverts to normal) would be changed to Partial Response if ascites remains present radiologically.

CR Complete response; NA Not applicable (only relevant if there were no target lesions at baseline or non-target lesions at baseline), NE Not evaluable; NED No Evidence of Diseases (only relevant if there were neither target lesions nor non-target lesions at baseline); PD Progressive disease; PR Partial response; SD Stable disease; TL Target Lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For patients with TLs (at baseline): complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), or not evaluable (NE)
- For patients with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For patients with no disease at baseline: NED (no evidence of disease; available as an option in the electronic case report form), PD, or NE

Evaluation of scans subsequent to RECIST 1.1-defined progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the Investigator for patient management and further treatment decisions, and since the published RECIST 1.1 criteria (Eisenhauer 2009) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined PD, supplemental instructions for Investigators on how to evaluate these follow-up scans are provided below. An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if *any* of the following criteria are met in the subsequent follow-up scan:

- ≥20% increase and at least a 5-mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥5 mm in the sum of diameters at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of previously new lesions (pre-existing new lesions) at the follow-up scan timepoint compared with the immediate prior timepoint
- additional brand-new unequivocal lesions at the follow-up scan timepoint

References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Durvalumab weight-based dose calculation

For durvalumab dosing done depending on patient weight. Weight-based dosing should be utilized for patients ≤30 kg:

1. Dose: X mg/kg

2. Patient weight: Y kg

3. Dose for patient: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL).

5. The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1. Dose: 20 mg/kg

2. Patient weight: 30 kg

3. Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

5. The number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

Appendix G Abbreviations

Abbreviation or special term	Explanation
12mOS	Overall survival at 12 months after inclusion
18mOS	Overall survival at 18 months after inclusion
6mOS	Overall survival at 6 months after inclusion
12mPFS	Progression-Free survival at 12 months after inclusion
6mPFS	Progression-Free survival at 6 months after inclusion
ADA	Anti-drug antibody
AE	adverse event
AESI	Adverse event of special inter
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUCss	Area under the plasma 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
CI	Confidence interval
CR	Complete response
CRF	Case report form (electronic/paper)
CRO	Contract Research Organization
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
CXCL	Chemokine (C-X-C motif) ligand
DAE	Discontinuation of investigational product due to adverse event
DCR	Disease control rate

Abbreviation or special term	Explanation
DL1	Dose level 1
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
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
ES	Extensive-stage
EORTC	European Organisation for Research and Treatment of Cancer
EP	Etoposide and platinum-based chemotherapy
ESMO	European Society for Medical Oncology
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
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

Abbreviation or special term	Explanation
imAE	Immune-mediated adverse event
IP	Investigational product
IRB	Institutional Review Board, synonymous to Ethics Committee (EC) and
IEC	Independent Ethics Committee (IEC)
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent to treat
IV	Intravenous
IWRS	interactive web response system
LD	Limited-stage disease
LIMS	laboratory information management system
LSLV	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
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
PI	Principal Investigator
PK	Pharmacokinetic(s)

Abbreviation or special term	Explanation
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
q4w	Every 4 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
TIL	Tumor-infiltrating lymphocyte
TL	Target lesion
ULN	Upper limit of normal
US	United States
VT	Verbatim Term
WBDC	web based data capture

Appendix H EORTC QLQ-C30 questionnaire

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

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

Appendix I EORTC QLQ-LC13 questionnaire

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.

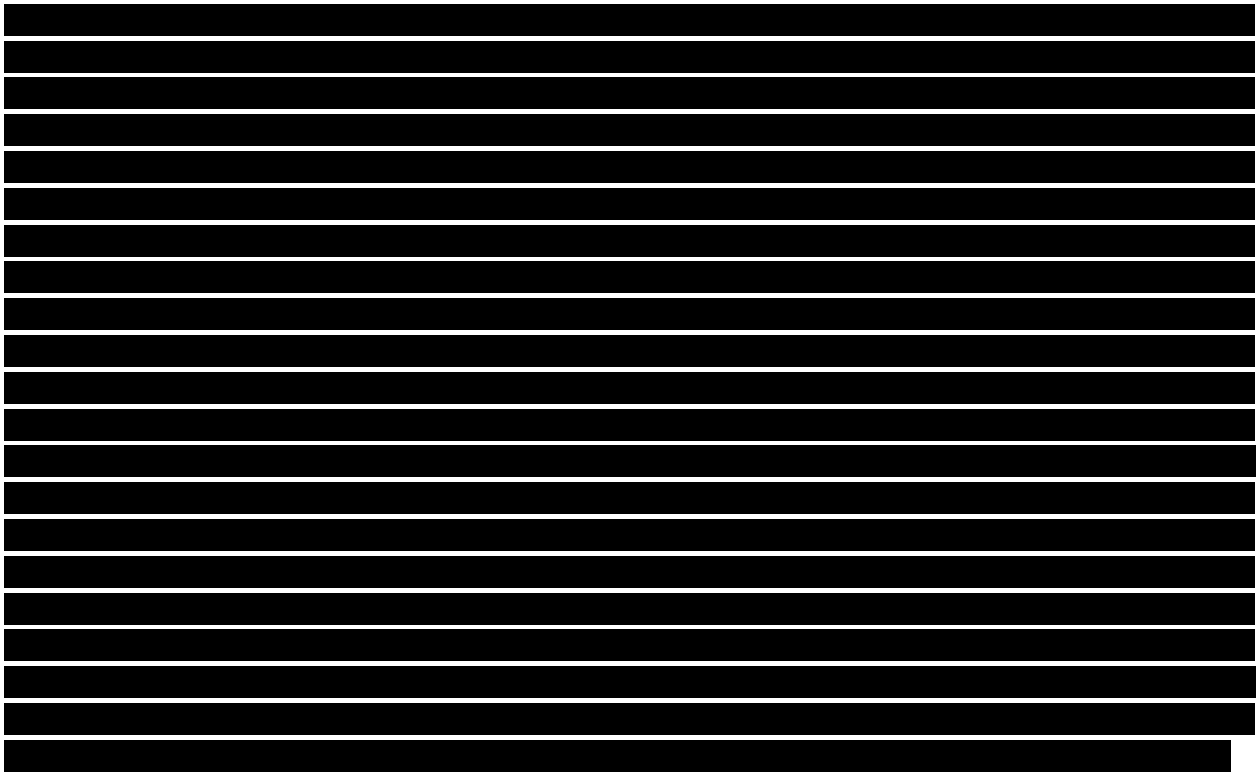
During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	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

Appendix J Discovery of biomarkers to predict benefit from chemoimmunotherapy in SCLC using digital spatial profiling

1. Background

Small cell lung cancer (SCLC) represents about 10 to 15 % of all lung cancers. It is strongly associated with tobacco exposure and typically follows an aggressive clinical course, characterized by early metastatic spread and rapid tumor growth (Gazdar et al., 2017). Platinum-based chemotherapy is the cornerstone of treatment of extensive stage SCLC. Despite initial objective responses in the majority of these patients, responses are not durable, and the median overall survival (OS) in this setting is about 11 months (Gazdar et al., 2017). The most notable recent clinical progress against SCLC has centered around immunotherapy with PD-1 checkpoint blockade. Atezolizumab and durvalumab added to first-line platinum-based chemotherapy have demonstrated a significant albeit modest 2-month increment in median OS in two randomized phase IIItrials (Horn et al., 2018; Paz-Ares et al., 2019).

However, despite this improvement in OS, only a small minority of patients demonstrate durable benefit, and biomarkers to identify these patients are currently lacking. PD-L1 expression, assessed by conventional chromogenic immunohistochemistry, and tumor mutational burden (TMB), are the only biomarkers that have been studied as potential predictors of response to PD-1 checkpoint blockade in SCLC. To date, none of them have shown consistent association with benefit from these drugs, and thus they are not approved for clinical use.



2. Objectives

Primary objective

[redacted]

Secondary objectives

[redacted]

3. Methods

[redacted]

[redacted]

[redacted]

Appendix K [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] in combination with platinum and etoposide and their relation with the toxicity and efficacy.

MATERIAL & METHODS

Patients

Patients with extensive disease SCLC included in the CANTABRICO trial and treated with first line treatment with durvalumab in combination with platinum and etoposide will be prospectively included in this study. Written informed consent will be obtained from each patient after the approval of the study by the Institutional Ethics Committee.

Patients‘ data will be collected from the CRF of the trial.

Patients will be included from 35 centers.

[redacted]

[redacted]

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov test will be used to analyze data with normal distribution. Normal distributed variables will be reported as mean ± standard error of mean (s.e.m.). To describe our population, numbers and percentages will be used for qualitative variables, while the median (interquartile ranges, IQR) will be calculated for ordinal and quantitative variables with an asymmetric distribution. Comparisons between groups will be tested with the Student‘s t or the Mann-Whitney test, according to a Gaussian distribution. ANOVA and Kruskal-Wallis tests will be used for comparisons between more than two groups. Fisher and Chi-square tests will be used for the comparison of frequencies. Correlation analyses will be carried out with Pearson‘s or Spearman correlations. All p values will be based on a 2-sided hypothesis, and those under 0.05 will be considered statistically significant. All the analyses will be performed using Graph Pad Prism 7 software.

Appendix L Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 17 November 2020.

See in a separate document.