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

Sponsor: AstraZeneca

AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT Number: 2020-005537-32

Protocol Number: 2.0

Amendment Number: 1

Study Intervention: Durvalumab in Combination with Platinum and Etoposide

Study Phase: Phase 3b

Short Title: Phase IIIb Study of Durvalumab in Combination with Platinum and Etoposide for the First Line Treatment of Extensive-stage Small Cell Lung Cancer Patients.

Acronym: LUMINANCE

Study Clinical Lead: AstraZeneca study physician. Name and contact information will be provided separately.

International Co-ordinating Investigator: PPD
PPD

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 2.0	06 August 2021
Version 1.0	25 November 2020

Amendment 1 (06 August 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The previous Clinical Study Protocol (CSP) version, version 1.0, dated 25 November 2020 was updated to implement changes requested by the regulatory authorities and other changes as per revised AstraZeneca CSP template. The updates are summarized below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Schedule of Activities (SoA)	In the 3rd point (For Durvalumab), the duration between 2 consecutive doses of durvalumab was modified.	For clarity	Non-substantial
	In Table 1, the IMPs were listed in the same order as the order of IMP administration per the protocol. Footnote 'a' updated to included the duration between 2 consecutive doses of durvalumab. Footnote 'q' updated to include details of IMP administration. Footnote 't' revised to clarify that the infusion is for etoposide.	To be consistent with order of administration as per protocol and for clarity	Non-substantial
Section 1.1 Schedule of Activities (SoA)	In Table 2, footnote g clarification that additional radiological procedures are not mandatory was included.	This clarification was requested by ethics committee	Non-substantial
Section 1.2: Synopsis	The estimated dates for first patient enrollment and last patient completion was updated.	Update on study coduct timelines	Non-substantial
Section 2.3.2.1: Durvalumab	Rash/dermatitis (including pemphigoid) and immune	Updated to align with current approved version of the	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	thrombocytopenia were added to the risks with durvalumab.	Investigators Brochure, informed consent form and revised protocol template	
Section: 2.3.2.1: Durvalumab	The events cough, dyspnea and nausea were removed from the list of frequent AEs with durvalumab in monotherapy clinical studies.	Update of the durvalumab safety data	Substantial
	A reference to Dosing Modification and Toxicity Management guidelines for durvalumab monotherapy or in combination with other products was added.	For clarity	Non-substantial
Section 4.1: Overall Design Corresponding change to Section 1.2: Synopsis, Section 1.3: Schema	The list of countries in which the study is conducted was updated	Study will not be conducted in the United Kingdom and will be conducted in Turkey.	Substantial
	The number of platinum (cisplatin or carboplatin) plus etoposide cycles was changed from “4 to 6” to "up to 4 to 6 cycles” in treatments and treatment duration. The corresponding update made in Figure 1 and Table 8.	For clarity	Substantial
Section 4.1.1: Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Details on study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis were added.	To provide details regarding the conduct of the study in case of study disruptions due to cases of civil crisis, natural disaster, or public health crisis, including COVID-19 outbreak	Substantial
Section 5.1: Inclusion Criteria	Inclusion criterion #3 was revised.	To clarify that the genetic analysis is optional	Non-substantial
Section 5.1: Inclusion Criteria	Inclusion Criteria # 10 updated. Creatinine Clearance values revised and clarified to include Etoposide treatment.	As requested by regulatory authority	Substantial
Section 5.2: Exclusion Criteria	Exclusion criterion #14 was revised to extend the period when live vaccines are not allowed from 30 days to 90 days after last dose of IMP.	As requested by regulatory authority	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.2: Exclusion Criteria	Exclusion criterion #16 was revised to state that 'Patient who previously received immunotherapy agents including anti PD-1/anti PD-L1 are not eligible' and remove sub-bullets with additional conditions.	For consistency with inclusion criterion # 9	Non-substantial
Section 5.2: Exclusion Criteria	Exclusion criterion #20 defined the period when contraception is required to 180 days after last dose of etoposide.	As requested by regulatory authority	Substantial
Section 5.3: Lifestyle Restrictions	Contraception requirements were updated. Highly effective methods of contraception provided in Table 4 updated.	For consistency with exclusion criterion #20 and update based on revised protocol template for safety reasons.	Substantial
	Lifestyle restrictions regarding sun exposure were added.	Update based on revised protocol template for safety reasons	Substantial
Section 6.1.1.1: Durvalumab (MEDI4736)	Deleted details about blinding of IV bag.	To correct an error, as this is an open-label study.	Substantial
	Infusion window of ± 10 minutes included for durvalumab infusion.	Update based on revised protocol template for safety reasons	Substantial
Section 6.1.2: Dose and Treatment Regimens	In Table 6, an explanation was added that etoposide will be administered daily for three consecutive days.	For clarity	Non-substantial
Section 6.4 Concomitant Therapy	The duration of recording concomitant medications included. Text was revised to extend the period when live vaccines are not allowed to 90 days after last dose of IMP. Tables 9 and 10 were deleted and a reference was made to Tables 17, 18 and 19 in newly added Appendix H (Concomitant Medications).	Refer to Appendix H	Substantial
Section 8.1.1: Survival Assessments	Incorrect reference to 'Table 1' was replaced by reference to 'Table 2. Clarification on how patients will be censored at the date cutoff.	To provide the correct reference and for clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.2.3: Vital Signs	A time window was added for the duration of infusion.	For consistency with duration of infusion in Section 6.1.1.1	Non-substantial
Appendix A Regulatory, Ethical and Study Oversight Considerations	Regulatory reporting requirements for serious adverse events revised, details on voluntary participation of patients explained and details on rescreening was included.	Update based on revised protocol template for safety reasons	Substantial
Appendix F Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)	In Table 13, clarification to footnote information that additional radiological procedures are not mandatory was included.	This clarification was requested by ethics committee	Non-substantial
Appendix G CCI	A footnote was added below the CCI specimen to clarify patient initials and date of birth will not be collected.	The clarification was requested by ethics committee	Non-substantial
Appendix H: Concomitant Medications:	Details previously provided in Section 6.4 were moved to a newly created appendix and supportive medications/therapies included.	Update as per revised protocol template and for safety reasons	Substantial
Appendix I: Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Additional details on study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis (and in particular COVID-19) was provided.	To provide guidance regarding the conduct of the study in case of study disruptions due to cases of civil crisis, natural disaster, or public health crisis, including COVID-19 outbreak	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The procedures for the screening and treatment periods in this study are presented in Table 1 and the procedures for the follow-up period are presented in Table 2.

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

For Durvalumab

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related adverse event (AE). In the event that durvalumab is discontinued or delayed as part of the toxicity management guidance, EP (platinum [cisplatin or carboplatin] plus etoposide) should still be administered as scheduled.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST 1.1]). It is recommended that subsequent time between 2 consecutive doses should not be less than 21 days, based on the half-life of durvalumab (see current Investigator Brochure [IB] for durvalumab).

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

- Patients may delay and subsequently resume dosing per local standard clinical practice.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible. In the event that EP is delayed, durvalumab should also be delayed and to be resumed as soon as feasible. Every effort should be made to ensure patients receive at least 4 cycles of EP, if conditions allow.

Table 1 Schedule of assessments and screening for durvalumab + EP treatment

	Screening	During Chemotherapy 1 cycle = 3 weeks (21 days) [a]					Post Chemotherapy 1 cycle = 4 weeks (28 days)	
		C1	C2	C3	C4	C5 and C6 [a]	C7 to PD	
Visit Window	**Day -28 to Day -1**	**0**	**±3 days unless dosing needs to be held for toxicity reasons**					
Week	**Weeks -4 to Week -1**	**0**	**3**	**6**	**9**	**12 [a] / 15 [a]**	**q4w**	**For details, see Section**
Informed Consent								
Informed consent: study procedures [b]	X							5.1
CCI [redacted]	X							5.1
Study procedures								
Physical exam (full)	X							8.2.2
Targeted physical exam [c]		X	X	X	X	X	X	8.2.2
Medical history [d]	X							
Vital signs [e]	X	X	X	X	X	X	X	8.2.3
ECG [f]	X	As clinically indicated						8.2.4
Concomitant medications		<----------					---------->	6.4
Demography, including baseline characteristics and tobacco use	X							5.1
Eligibility criteria	X	X						5.1, 5.2
Laboratory Assessments								
Clinical chemistry [g]	X	X [h]	X	X	X	X	X	Table 9
Hematology [g]	X	X [h]	X	X	X	X	X	Table 10
Coagulation [i]		X						Table 10
TSH [j], (reflex free T3 or free T4 [k])	X	X	X	X	X	X	X	Table 9
Urinalysis	X	As clinically indicated						Table 11
Hepatitis B and C and HIV	X							8.2.7
Pregnancy test [l]	X	X	X	X	X	X	X	8.2.1
Monitoring								
WHO/ECOG performance status	X	X	X	X	X	X	X	8.2.5
AE/SAE assessment [m]		<----------					---------->	8.3
Assessment of early toxicities (phone call) [n]		X	X	X				8.2.5

	Screening	During Chemotherapy 1 cycle = 3 weeks (21 days) [a]						Post Chemotherapy 1 cycle = 4 weeks (28 days)	
		C1	C2	C3	C4	C5 and C6 [a]		C7 to PD	
Visit Window	**Day -28 to Day -1**	**0**	**±3 days unless dosing needs to be held for toxicity reasons**						
Week	**Weeks -4 to Week -1**	**0**	**3**	**6**	**9**	**12 [a]**	**15 [a]**	**q4w**	**For details, see Section**
IMP administration [o]									
Durvalumab [p]		X	X	X	X	X		X	6.1.1.1
Carboplatin or cisplatin [q,r]		X	X	X	X [s]	X			6.1.1.2
Etoposide [q,t]		X	X	X	X [s]	X			6.1.1.2
Efficacy evaluations									
Tumor assessment (according to RECIST 1.1) [u]	X			X ± 7 days		X (C5) ± 7 days		X Every 8 weeks ± 1 week until PD	8.1, Appendix F
CT/MRI of brain, chest, abdomen [v]	X								
CCI									
CCI									
CCI									
CCI									
CCI									
CCI									
CCI									

[a] C5 and C6 of chemotherapy per investigator discretion. The first dose of durvalumab maintenance treatment will be administered 3 weeks after the last dose of chemotherapy. Subsequent doses of durvalumab will be administered on a q4w schedule until PD. It is recommended that subsequent time between 2 consecutive doses should not be less than 21 days, based on the half-life of durvalumab.

[b] Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. All patients will be required to provide consent to supply an archival sample of their tumor. This consent is included in the main patient ICF. 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 results and screening imaging results must have been obtained within 28 days of the first dose.

[c] Targeted physical examination are to be utilized by the Investigator on the basis of clinical observations and symptomatology.

[d] Medical history related to primary indication and clinically significant medical history.

[e] Body weight is recorded at each visit along with vital signs. Height is recorded at screening only. 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.

[f] Any clinically significant abnormalities detected require triplicate ECG results. Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. 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.

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

[h] 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.

[i] Coagulation tests are only performed at baseline on Day 1 (unless performed within 3 days prior to Day 1) and as clinically indicated.

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

[k] 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.

[l] 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 prior to every dosing visit (within 3 calendar days prior to dosing). 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.

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

[n] For the first 3 cycles, patients should be contacted 1 week (±1 day) after receiving the IMP to ensure early identification and management of toxicities. This contact should be documented in the medical records.

[o] A window of up to 3 days is permitted between last screening assessments and first dose of IMP. Last assessments on Friday and dosing on Monday will be accepted.

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

[q] Durvalumab is infused first followed by platinum (carboplatin or cisplatin) and etoposide on Day 1 of each combination cycle; etoposide will also be administered on days 2 and 3 of each cycle, up until a maximum of 6 cycles has been reached. The interval between each infusion will be per standard of care.

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

[s] EP q3w up to 4 cycles; extension into Weeks 12 and 15 is at the investigators' discretion, CCI collection q4w until PD are required irrespective of the number of cycles of EP given.

[t] Infuse etoposide over 0.5 to 1 hour .

[u] See Section 6.1.3, Section 8.1 for additional details relevant to image acquisition, RECIST 1.1 assessments, and evaluation of scans after RECIST 1.1-defined progression. Note: tumor evaluation at Week 6±1 weeks, at Week 12 ± 1 weeks and q8w thereafter.

[v] Baseline CT/MRI results of the brain, chest and abdomen (including liver and adrenal glands) within 28 days prior to the treatment initiation.

[w] CCI [redacted]

x CCI

y CCI

z CCI

aa CCI

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.
AE: adverse event; C: Cycle; CT: computed tomography; CCI
ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; CCI
CCI
CCI
; EP: platinum (cisplatin or carboplatin) plus etoposide; CCI ; HIV: human immunodeficiency virus; ICF: informed consent form; IMP: investigational medicinal product; LFT: liver function test; MRI: magnetic resonance imaging; PD: progression of disease; CCI ; qXw: every X weeks; RECIST: Response Evaluation Criteria in Solid Tumours version 1.1; SAE: serious adverse event; T3: Triiodothyronine; T4: Thyroxine; TSH: thyroid-stimulating hormone; WHO: World Health Organisation.

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

	Time since last dose of IMP								
	Day (±3)	Months (±1 week)						12 months and every 3 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]								8.2.5
Subsequent anticancer therapy [c]	<--------->								8.1
Survival status [d]		X	X	X	X	X	X	X	8.1
Hematology	X	X	X						8.2.1
Clinical chemistry	X	X	X						8.2.1
Urinalysis	As clinically indicated								8.2.1
TSH (reflex free T3 or free T4) [e]	X	X	X						8.2.1
CCI	CCI								CCI
CCI	CCI								CCI
CCI	CCI								CCI
CCI	CCI	CCI	CCI						CCI
Tumor assessment (RECIST 1.1) [g]	Every 8 weeks ±1 week until PD								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 IMP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.

[d] 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 IMP must be recorded in the eCRF.

[e] 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.

[f] CCI

[g] See Section 6.1.3, Section 8.1, for additional details relevant to image acquisition, RECIST 1.1 assessments, and evaluation of scans after RECIST 1.1-defined progression. CT/MRI at baseline should consider brain scan due to very common involvement of central nervous system; further CT/MRI evaluations should be according to the schedule and brain scan when clinically indicated. Additional radiological procedures such as PET/CT, bone scintigraphy and other X-rays (should be applied for non-RECIST assessments) when clinically indicated (not mandatory).

AE: adverse event; CT: computed tomography; CCI ; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; CCI CCI CCI CCI ; ES-SCLC: extensive-stage small cell lung cancer; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PD: progression of disease; CCI ; RECIST: Response Evaluation Criteria in Solid Tumours version 1.1; SAE: serious adverse event; T3: Triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; WHO: World Health Organisation.

1.2 Synopsis

Protocol Title:

A Phase IIIb, single-arm, multi-center, international study of durvalumab in combination with platinum and etoposide for the first line treatment of patients with extensive-stage small cell lung cancer (LUMINANCE)

Rationale:

Extensive-stage small cell lung cancer (ES-SCLC) is an aggressive malignancy and the prognosis remains poor despite favorable initial response to platinum-based chemotherapy, which has been the standard treatment for over 3 decades. Recently, immunotherapy targeting the programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) pathway has demonstrated clinical activity for patients with ES-SCLC, including as first-line treatment (Horn et al 2018, Paz-Ares et al 2019).

The Phase III, randomized open-label CASPIAN trial demonstrated a statistically significant and clinically meaningful improvement in overall survival with the addition of durvalumab to platinum (cisplatin or carboplatin) plus etoposide (EP) compared to EP alone as a first line treatment for patients with ES-SCLC. Consistent results were also observed for progression-free survival (PFS) and objective response rates, which also favored durvalumab + EP compared to EP alone (Paz-Ares et al 2019). These clinical benefits were observed in the context of a clinically relevant control arm that permitted the flexibility in platinum choice (carboplatin or cisplatin), up to 6 cycles of EP (consistent with routine clinical practice and compared with a maximum of 4 cycles in the durvalumab + EP arm) and the use of prophylactic cranial irradiation (PCI) at the investigator's discretion.

ES-SCLC patients often have rapidly progressive disease and a significant proportion of patients will have poor prognosis (Eastern Cooperation Oncology Group [ECOG] PS2 or higher) at diagnosis (Foster et al 2009). As is common with registrational Phase III studies, CASPIAN limited recruitment to those patients with good performance status (ECOG 0 or 1) and therefore little is currently known regarding the safety and efficacy of durvalumab + EP in patients with ECOG PS2. There also remains an unmet need for additional safety and efficacy data to help support and inform treatment decisions on the use of durvalumab + EP for unselected patients in real clinical practice, including in combination with up to 6 cycles of chemotherapy and/or the use of PCI.

Objectives and Endpoints

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

Objectives and Endpoints

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

Note: Toxicities will be classified as per NCI CTCAE grading system version 5.0. Analysis of ORR and DoR will be based upon Investigator assessment according to RECIST 1.1. Prior irradiated lesions may be considered measurable and selected as TLs providing they fulfil the other criteria for measurability.

Note: An AESI is an AE of scientific and medical interest specific to understanding of the IMP. AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy.

AE: adverse event; AESI: adverse event of special interest; DoR: duration of response; DOR12: proportion of patients remaining in response 12 months from the time of first documented objective response; CTCAE: Common Terminology Criteria for Adverse Events; CCI [redacted]; EP: platinum (cisplatin or carboplatin) plus etoposide; CCI [redacted]; imAE: immune-mediated adverse event; IMP: investigational medicinal product; NCI: National Cancer Institute; ORR: objective response rate; OS: overall survival; OS12: proportion of patients alive at 12 months from first date of treatment; CCI [redacted] 1; PFS: progression-free survival; PFS12: proportion of patients alive and progression-free at 12 months from first date of treatment; CCI [redacted]; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SAE: serious adverse event; CCI [redacted].

Overall Design:

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

Study Period:

Estimated date of first patient enrolled **Q3 2021**

Estimated date of last patient completed **Q4 2023**

Number of Patients:

Approximately 150 adult patients with ES-SCLC eligible for first line treatment with platinum-based chemotherapy will be enrolled for treatment.

Treatments and Treatment Duration:

All patients will receive durvalumab 1500 mg administered via intravenous (IV) infusion concurrently with platinum-based chemotherapy (Investigator's choice of cisplatin or carboplatin) and etoposide q3w starting on Week 0 for up to 4 to 6 cycles. Durvalumab monotherapy will be continued q4w post-chemotherapy until confirmed radiological disease progression.

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

- EP: the dose of cisplatin or carboplatin plus etoposide investigated will not exceed the product label dose for the given indication dose (cisplatin [75 to 80 mg/m^2] via IV infusion or carboplatin [area under the curve (AUC) 5-6 (For PS2 patients a dose of AUC 4 is allowed)] via IV infusion with etoposide [80 to 100 mg/m^2] via IV infusion).

- Prophylactic cranial irradiation may be delivered per investigator discretion and local practice.

Duration of Treatment

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

EP will be administered for up to 4 to 6 cycles for patients per investigator clinical decision.

Progression During Treatment

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined progression of disease (PD) may continue to receive treatment at the discretion of the Investigator and patient, after re-consenting for treatment through progression. 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 F. Patients with confirmed PD who continue to receive study treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit, and tumor assessments should continue on their regular imaging schedule for the duration of treatment. 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 F.

However, patients will not be permitted to continue immunotherapy if progression occurs after confirmed response (complete response [CR] or partial response [PR] as defined by RECIST 1.1) to immunotherapy treatment in the target lesions (TLs) (regardless of the appearance of new lesions) (ie, the response and progression events both occurred in the TLs while receiving immunotherapy during the same treatment period).

Follow up of Patients Post Discontinuation of Study Drug

Patients who have discontinued study treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy, will be followed up for AEs CCI [redacted] for 90 days after last dose of investigational medicinal product (IMP), and thereafter followed up with tumor assessments until RECIST 1.1-defined radiological PD plus an additional follow-up scan or until death (whichever comes first).

Survival

All patients in the study should be followed up for survival at months 2, 3, 4, 6, 8, 10, and 12 months following last dose of IMP, and then every 12 weeks until death, withdrawal of consent, or the end of the study.

Steering Committee

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

Statistical Methods

The primary objective of this study is to assess the safety and tolerability of durvalumab + EP, in terms of the incidence of Grade ≥ 3 AE and incidence of immune-mediated AE (imAE). A secondary objective of this study is to further assess the safety and tolerability of durvalumab + EP, in terms of all AEs, serious adverse events (SAEs), adverse events of special interest (AESIs) and AEs leading to treatment discontinuation.

The primary analysis, for safety, will be conducted approximately 6 months after the last patient is enrolled into the study and the final statistical analysis will be conducted after the last patient has had the opportunity to be followed up for a minimum of 12 months or 60% overall survival (OS) maturity, whichever occurs first.

Safety data will be summarized descriptively overall, by seriousness, by causality, and by maximum National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) grade. The exact 95% confidence intervals (CIs) around the incidence estimates of Grade ≥ 3 AEs and imAEs will be reported. Continuous variables will be summarised by the number of observations (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

The efficacy of first-line durvalumab + EP will be assessed as secondary objectives, in terms of OS, PFS, objective response rate (ORR), duration of response (DoR), proportion of patients alive at 12 months from first date of treatment (OS12), proportion of patients alive and progression-free at 12 months from first date of treatment (PFS12) and proportion of patients remaining in response 12 months from the time of first documented objective response (DoR12).
Time-to-event data will be summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% CIs. ORR (based on Investigator assessment) will be summarized descriptively, and the exact 95% CIs will be reported. Data will be reported for patients overall and separately for patients based on performance status (0 to 1 and 2).

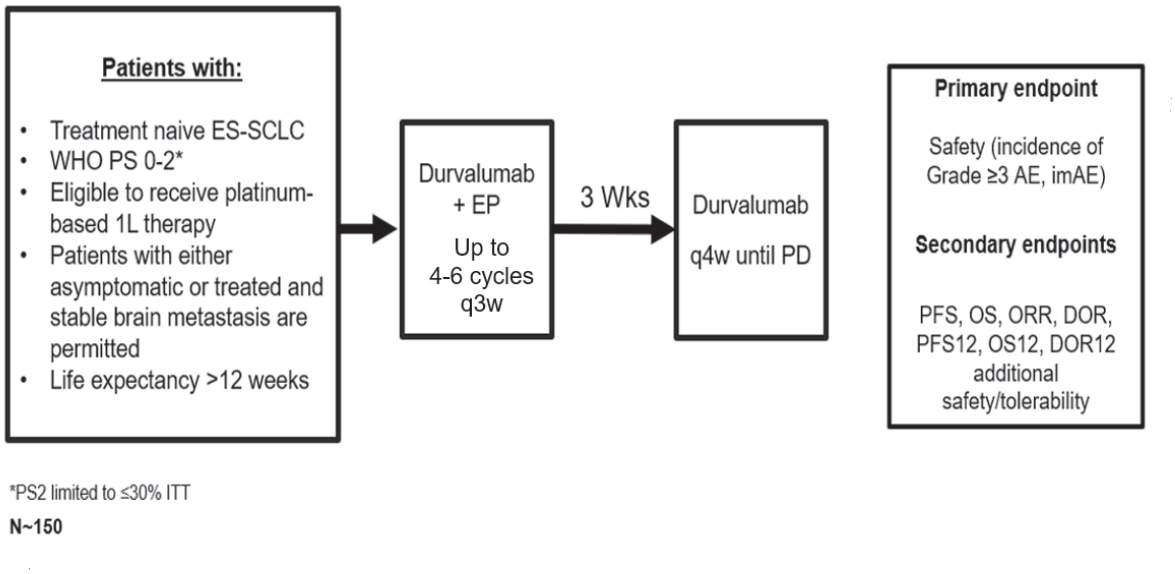
This is a safety study and no formal sample size calculation will be done. However, a total of approximately 150 patients will be treated with durvalumab plus platinum (cisplatin or carboplatin) plus etoposide. A maximum of 30% of all patients treated will have ECOG performance status of 2 at baseline (Cycle 1 Day 1). If the true incidence of Grade ≥3 AEs and imAEs in the overall population is approximately 70% and 20% respectively (rates observed in the CASPIAN Study were 65% and 20%, respectively), the sample size of 150 patients will provide a precision of ±7.6% with an exact binomial 95% CI of 62.0-77.2 for Grade ≥ 3 AEs, and a precision of ± 6.7% with an exact binomial 95% CI of 13.9, 27.3 for imAE.

There will be no formal interim analysis in this study.

1.3 Schema

The general study design is summarized in Figure 1.

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



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

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

2. INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades, with an estimated 2.1 million new cases in 2018, representing 11.6% of all new cancers. It was also the most common cause of death from cancer, with 1.76 million deaths (18.4% of the total) (GLOBOCAN 2018).

Small cell lung cancer (SCLC) represents approximately 13-17% of all newly diagnosed lung cancers (Oronsky et al 2017, Wang et al 2017). 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 development of widespread metastases. It is strongly associated with tobacco smoking and is also associated with an extremely high mutation rate (Peifer et al 2012, Alexandrov et al 2013, Byers and Rudin 2015).

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

For more than three decades, the standard first-line therapy for ES-SCLC consisted of four to six cycles of etoposide in combination with either cisplatin or carboplatin, without maintenance therapy (Pietanza et al 2015, Früh et al 2013, Rudin et al 2015, Japan Lung Cancer Society, 2018). Despite high initial response rates of approximately 78% (Rossi et al 2012, Fukuoka et al 1991), it is estimated that 80% of patients with LS and almost all patients with ES-SCLC will relapse or experience disease progression (Clark and Ihde 1998). Therefore, the prognosis for patients with 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).

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

Although the clinical efficacy between cisplatin and carboplatin may be indistinguishable, they differ in terms of cost and toxicity profiles.

Several large Phase III studies using EP as the comparator in this setting have consistently reported the median PFS between 4 to 6 months and median OS between 7 to 11 months (Slotman et al 2015). Recently published data with EP as the control arm in randomized Phase III studies is consistent with earlier trials, with median PFS of 4.3 to 4.4 months and median OS of 10.3 to 10.9 months (Reck et al. 2016; Horn et al 2018, Paz-Ares et al 2019) as first line treatment of ES-SCLC.

Recently, immunotherapy targeting the PD-1 and PD-L1 pathway has demonstrated clinical activity for patients with ES-SCLC, including as first-line treatment (Horn et al 2018, Paz-Ares et al 2019).

2.1 Study Rationale

ES-SCLC is an aggressive malignancy and the prognosis remains poor despite favorable initial response to platinum-based chemotherapy, which has been the standard treatment for over 3 decades. Recently, immunotherapy targeting the PD-1 and PD-L1 pathway has demonstrated clinical activity for patients with ES-SCLC, including as first-line treatment.

ES-SCLC patients often have rapidly progressive disease and a significant proportion of patients will have poor prognosis (ECOG PS2 or higher) at diagnosis (Foster et al 2009). As is common with registrational Phase III studies, CASPIAN limited recruitment to those patients with good performance status (ECOG 0 or 1) and therefore little is currently known regarding the safety and efficacy of durvalumab + EP in patients with ECOG PS2. There also remains an unmet need for additional safety and efficacy data to help support and inform treatment decisions on the use of durvalumab + EP for unselected patients in real clinical practice, including in combination with up to 6 cycles of chemotherapy and/or the use of PCI.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the IB.

2.2.1 Immunotherapies

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

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T cell activation. 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 (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 (MOA) 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, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition high mutational burden (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 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 NSCLC, 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.

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2 [PD-L2]) with PD-1 on T cells and CD80 (B7.1) on immune cells. 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 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 interferon-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 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. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

2.2.3 Durvalumab in Combination with Chemotherapy

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

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

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 trial that compared atezolizumab + etoposide/carboplatin (EC) with placebo + EC in the first line treatment of ES-SCLC (Horn et al 2018). The study demonstrated a statistically significant improvement in OS with the combination of atezolizumab + EC compared to placebo + EC (Horn et al 2018). CASPIAN was a randomized, open-label, Phase III trial that compared durvalumab, with or without tremelimumab, in combination with EP versus EP alone in treatment naïve patients with ES-SCLC. The CASPIAN trial demonstrated a statistically significant improvement in OS for durvalumab + EP compared to EP alone in first line treatment of ES-SCLC (Paz-Ares et al 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 et al 2020).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of durvalumab may be found in the IB.

2.3.1 Potential Benefits

2.3.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab monotherapy are based on the first-in-human, single-agent study (Study 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.

2.3.1.2 Durvalumab + Chemotherapy

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

The Phase III CASPIAN study demonstrated a statistically significant improvement in OS for durvalumab + EP compared to EP alone as first-line treatment for ES-SCLC at a pre-planned interim analysis with a HR of 0.73 (95% CI 0.59–0.91; p = 0.0047) (Paz-Ares et al 2019). The median overall survival was 13.0 months (95% CI 11.5–14.8) in the durvalumab plus EP group versus 10.3 months (95% CI, 9.3–11.2) in the EP alone group. The OS improvement with durvalumab plus EP was demonstrated across all pre-specified subgroups. The secondary endpoint of PFS was also improved with durvalumab plus EP versus EP (PFS HR: 0.78 [95% CI, 0.645–0.936]; median PFS, 5.1 vs. 5.4 months); the 12-month PFS rate was 17.5% vs. 4.7%, respectively. Durvalumab plus EP showed a 10% improvement in confirmed ORR compared to EP; 67.9% vs. 57.6%, respectively. The treatment effects of durvalumab + EP were sustained overtime compared to EP alone, as supported by the estimates of the 18 month OS rate, as well as the 12-month OS, PFS, and Duration of Response rates: 53.7% vs 39.8% of patients were alive at 12 months; an estimated 33.9% vs 24.7% of patients were alive at 18 months; and the 12-month PFS rate was 17.5% vs 4.7%, across the two groups, respectively.

2.3.2 Overall Risks

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

2.3.2.1 Durvalumab

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

inflammatory events including neuromuscular toxicities (eg, Guillain-Barre syndrome, myasthenia gravis).

In monotherapy clinical studies, AEs at an incidence of > 20% include events such as fatigue and decreased appetite. 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 CTCAE Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.4).

Information on all identified and potential risks with durvalumab and a detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB and the Dosing Modification and Toxicity Management Guidelines for Durvalumab Monotherapy or in Combination with Other Products.

2.3.2.2 Durvalumab + 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 et al 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.

Immune-mediated AEs, defined as an event that is associated with drug exposure and consistent with an immune-mediated MOA, 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.

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.

2.3.3 Overall Benefit/Risk

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

Recently, immune checkpoint inhibitors targeting the PD-1 and PD-L1 pathway have demonstrated clinical activity across multiple lines of therapy for patients with ES-SCLC.

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-SCLC over EP alone.

Taken together, the overall benefit/risk assessment supports the proposed study to further evaluate the safety and efficacy of durvalumab + EP as a first line treatment for ES-SCLC.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints/variables are listed in Table 3.

Table 3 Study objectives

Primary Objective:	**Endpoint/Variable:**
To assess the safety and tolerability profile of durvalumab + EP treatment	Incidence of Grade ≥ 3 AE Incidence of imAEs
Secondary Objective:	**Endpoint/Variable:**
To assess the efficacy of durvalumab + EP treatment	PFS, ORR, DoR, DoR12, and PFS12 using site Investigator assessments according to RECIST 1.1 OS and OS12
To further assess the safety and tolerability profile of durvalumab + EP, including all AEs	Incidence of AEs, SAEs, AESIs, AE resulting in treatment discontinuation, and laboratory findings including clinical chemistry, hematology and urinalysis
Exploratory Objective:	**Endpoint/Variable:**
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

Table 3 Study objectives

CCI	CCI

Note: Toxicities will be classified as per NCI CTCAE grading system version 5.0. Analysis of ORR and DoR will be based upon Investigator assessment according to RECIST 1.1. Prior irradiated lesions may be considered measurable and selected as TLs providing they fulfill the other criteria for measurability.

Note: An AESI is an AE of scientific and medical interest specific to understanding of the IMP. AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy.

AE: adverse event; AESI: adverse event of special interest; DoR: duration of response; DoR12: proportion of patients remaining in response 12 months from the time of first documented objective response; CTCAE: Common Terminology Criteria for Adverse Events; CCI CCI CCI CCI ; EP: platinum (cisplatin or carboplatin) plus etoposide; CCI CCI imAE: immune-mediated adverse events; IMP: investigational product; NCI: National Cancer Institute; ORR: objective response rate; OS: overall survival; OS12: proportion of patients alive at 12 months from first date of treatment; CCI ; PFS: progression-free survival; PFS12: proportion of patients alive and progression-free at 12 months from date of first treatment; CCI ; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SAE: serious adverse event; CCI .

4. STUDY DESIGN

4.1 Overall Design

This is a Phase IIIb, open-label, single-arm, multi-center, international study to evaluate the safety and tolerability profile of durvalumab plus platinum (cisplatin or carboplatin) plus etoposide (EP) in patients with ES-SCLC. An umet need remains for additional safety and efficacy data to help support and inform treatment decisions on the use of durvalumab + EP for unselected patients in real clinical practice, including patients with Eastern Cooperative Oncology Group (ECOG) PS of 2, in combination with up to 6 cycles of chemotherapy and/or the use of PCI. Patients will receive durvalumab plus EP for up to 4-6 cycles (investigators choice, q3w) and then durvalumab q4w until PD.

Approximately 150 patients will be treated with the study drug in North America, Europe and Turkey. Patients must have histologically- or cytologically-documented ES-SCLC and be

treatment naïve. Patients must be deemed to be eligible for etoposide and platinum-based chemotherapy per Investigator assessment.

The primary analysis, for safety, will be conducted approximately 6 months after the last patient is enrolled into the study and the final statistical analysis will be conducted after the last patient has had the opportunity to be followed up for a minimum of 12 months or 60% OS maturity, whichever occurs first.

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.

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

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

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

- Obtaining [consent/reconsent] for the mitigation procedures (note, in the case of verbal [consent/reconsent], the informed consent form [ICF] should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated study clinical lead.
- Remote visit: Performed by a site qualified health care professional (HCP) or HCP provided by a third-party vendor.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

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

4.2 Scientific Rationale for Study Design

CASPIAN demonstrated a statistically significant and clinically meaningful improvement in overall survival with durvalumab + EP versus EP alone, with an HR of 0.73 (95% CI 0.59–0.91; p = 0.0047). The overall safety profile in CASPIAN was similar between the two groups, with similar frequencies of grade 3 or 4 AEs, AEs leading to discontinuation, and AEs leading to death.

This study is designed to further evaluate the safety and efficacy of durvalumab plus EP in an ES-SCLC patient population that is more reflective of real-world clinical practice. Given the advanced presentation of ES-SCLC at the time of diagnosis, a need for additional safety data on the use of durvalumab on unselected populations exists, including in the sub-population of World Health Organization (WHO)/ECOG PS 2 patients, who have not been representatively included in pivotal studies.

The primary objective of this study is to assess the safety of durvalumab + EP, as defined by the incidence of Grade 3 and higher AEs and the incidence of imAEs. The specific nature of toxicities (SAEs, AEs, adverse events of special interest [AESIs], imAEs), interventions and treatment, and outcome of treatment will also be evaluated.

A secondary aim of this study is to evaluate the efficacy of durvalumab + EP in terms of ORR, PFS, and OS. Antitumor activity will be assessed according to RECIST 1.1 guidelines (see Section 8.1). The tumor-based efficacy analyses will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

CCI

CCI

4.3 Justification for Dose

4.3.1 Durvalumab Dose and Treatment Regimen Justification

4.3.1.1 Durvalumab Monotherapy 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).

Pharmacokinetic/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 AUCss (4 weeks). Median Cmax,ss is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median Ctrough,ss is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of anti-drug antibody 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 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.

4.3.1.2 Rationale 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 mAbs 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.

4.3.2 Rationale 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 et al 2019). Likewise, the dose and schedule of platinum (cisplatin or carboplatin) and etoposide are consistent with clinical practice guidelines (Paz-Ares et al 2019).

This trial will allow up to a maximum of 6 cycles of durvalumab + EP. 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 (National Comprehensive Cancer Network 2019, ESMO Clinical Practice Guidelines). In the CASPIAN trial, 57% of patients in the control arm received 6 cycles of EP (Paz-Ares et al 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.

4.4 End 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.

In the event that a rollover or safety extension study is available at the time of the final data cut-off (DCO) and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

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 must meet all of the inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2) for this study at the screening visits. Under no circumstances will there be exceptions to this rule.

In this protocol, "enrolled" patients are defined as those who sign informed consent.

For procedures for withdrawal of incorrectly enrolled patients see Section 6.2.2.

5.1 Inclusion Criteria

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

Informed Consent

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

2. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

3. Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative.

The ICF process is described in Appendix A 3.

Age

4. Age ≥ 18 years at the time of Screening.

Type of Patient and Disease Characteristics

5. Histologically- or cytologically-documented ES-SCLC (stage IV [T any, N any, M1 a/b], or with T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan, according to American Joint Committee on Cancer Stage 8th edition).

    – Brain metastases; must be asymptomatic or treated and stable off steroids and anticonvulsants for at least 1 month prior to study treatment.

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

7. WHO/ ECOG Performance Status of 0 to 2 at enrollment.

   – Note: Patients with PS2 will be limited to a maximum of 30% of the total study population; once this limit is met, additional enrolled patients must have PS 0-1.

8. Baseline computed tomography (CT) / magnetic resonance imaging (MRI) results of the brain, chest and abdomen (including liver and adrenal glands) within 28 days prior to the treatment initiation.

9. No prior exposure to immune-mediated therapy including, but not limited to, other anti- CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.

10. Adequate organ and marrow function as defined below:

   – Hemoglobin ≥ 9.0 g/dL.

   – Absolute neutrophil count ≥ 1.5×10^9/L (use of granulocyte colony-stimulating factor is not permitted at screening).

   – Platelet count ≥ 100×10^9/L.

   – Serum bilirubin ≤ 1.5 × the upper limit of normal (ULN).

   – In patients without hepatic metastasis: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN.

   – In patients with hepatic metastases, ALT and AST ≤ 5 × ULN.

   – Measured or calculated creatinine clearance: > 60 mL/min for patients planned to be treated with etoposide + cisplatin and > 50 mL/min for patients planned to be treated with etoposide + carboplatin as determined by Cockcroft-Gault:

     Males:

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

     Females:

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

11. Life expectancy ≥ 12 weeks at Day 1.

Weight

12. Body weight > 30 kg.

Sex

13. Male and/or female

Reproduction

14. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause.

    The following age-specific requirements apply:

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

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

5.2 Exclusion Criteria

Medical Conditions

1. History of allogeneic organ transplantation.

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

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

3. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

4. History of another primary malignancy except for:

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

5. History of leptomeningeal carcinomatosis.

6. History of active primary immunodeficiency.

7. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** virus (HBV) (known positive HBV surface antigen [HBsAg] result), **hepatitis C** virus (HBC), or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

8. Any unresolved toxicity CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, lymphopenia and the laboratory values defined in the inclusion criteria:

- Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

9. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

Prior/Concomitant Therapy

10. Received prior systemic therapy for ES-SCLC.

    - Patients who have received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle at the time of diagnosis of ES-SCLC.

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

12. Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

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

14. Receipt of live attenuated vaccine within 30 days prior to the first dose of IMP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IMP and up to 90 days after the last dose of IMP.

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

16. Patients who have received prior immunotherapy agents including anti-PD-1 or anti PD-L1

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

    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection).

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.

- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

Prior/Concurrent Clinical Study Experience

18. Participation in another clinical study with an investigational product administered in the last 4 weeks.

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

Diagnostic Assessments

Not applicable.

Other Exclusions

20. Female patients who are pregnant or breastfeeding, or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab and 180 days after the last dose of etoposide.

21. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

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

For procedures for withdrawal of incorrectly enrolled patients, see Section 6.2.2.

5.3 Lifestyle Restrictions

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

1. Female patient of childbearing potential.

   - Female patients of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study drugs) and intend to be sexually active with a non sterilized male partner must use at least 1 **highly** effective method of contraception (Table 4). They should have been stable on their chosen method of birth control

for a minimum of 90 days before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab and 180 days after the last dose of etoposide). 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 (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) 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 and 180 days after the last dose of etoposide). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation or banking throughout this period.

- Vasectomised males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

- Even if the female partner is pregnant, male patients should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing foetus from drug in ejaculate.

- 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.

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
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the patient) • Vasectomised sexual partner (with patient assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion • Intrauterine device (provided coils are copper banded)	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)[a] • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a] • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Mini pill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] Hormonal methods not prone to drug-drug interactions.

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. During study treatment and for 4 weeks after the last dose of study drug, patients should be advised to avoid prolonged exposure to the sun, wear protective clothing including a hat, and seek shade from the sun as much as possible; in addition, SP30+

sunscreen should be used. Exposure to other sources of ultraviolet light including sun beds and tanning booths, etc, should be avoided.

5. Restrictions relating to concomitant medications are described in Appendix H 1.

5.4 Screen Failures

Screen failures are patients who do not fulfill the eligibility criteria for the study. These patients should have the reason for study withdrawal recorded as "screen failure" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures. Patients may be rescreened a single time. If a patient who has failed screening is rescreened, a new E-code must be assigned. Patients will reconfirm their consent to participate in the study by re-signing and dating their original consent form(s), next to their initial signature and date.

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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs and concomitant medications used due to the SAEs.

6. STUDY TREATMENTS

6.1 Treatments Administered

6.1.1 Investigational Products

AstraZeneca will supply durvalumab (MEDI4736), whereas the EP treatments will be supplied locally (Table 5). Ancillary supplies required for infusion will also be locally provided (eg, saline bags, infusion lines).

Table 5 Study treatments

	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Study treatment name:	Durvalumab (MEDI4736)	Etoposide	Carboplatin	Cisplatin
Dosage formulation:	500-mg vial solution for infusion after dilution, 50 mg/mL	(as sourced locally)	(as sourced locally)	(as sourced locally)
Route of administration:	IV	IV	IV	IV
Dosing instructions:	Patients will receive durvalumab (1500 mg) via IV infusion over 60 minutes on Day 1 of each cycle.			

Table 5 Study treatments

	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Packaging and labelling:	Study treatment will be provided in vials and cartons (3 × vials per carton) Each vial and carton will be labelled in accordance with GMP Annex 13 and per country regulatory requirement [a]	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 "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

GMP: Good Manufacturing Practice; IV: intravenous.

6.1.1.1 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 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 IMP 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 ± 10 minutes, however if there are interruptions during the infusion, the total allowed infusion time should not exceed 8 hours at room temperature with the infusion bag maintained at room temperature, otherwise a new dose must be prepared from new vials.

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.

6.1.1.2 Platinum (Cisplatin or Carboplatin) plus Etoposide

EP will be locally sourced and will be administered according to prescribing information or treatment guidance in general use by the Investigating site, including the sequence of drug administration.

6.1.1.3 Order of Administration

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

A 60-minute observation period is recommended after durvalumab is administered at least for cycle 1.

If no issues are seen after durvalumab is given during the first cycle, it is recommended to reduce the observation period after durvalumab administration to 30 minutes for subsequent cycles.

This will then be followed by carboplatin or cisplatin as an IV infusion, followed by etoposide sequentially administered by an IV infusion on Day 1 of each combination cycle; etoposide will also be administered on days 2, and 3 of each cycle, up until a maximum of 6 cycles has been reached. Duration of infusions for chemotherapy agents will be per local practice.

6.1.2 Dose and Treatment Regimens

Dose and treatment regimens during and post chemotherapy are described in Table 6 and Table 7, respectively. The dosing schedule is provided in Table 8.

Table 6 Dose and treatment regimen during chemotherapy

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 min	Up to 4 to 6 doses with EP q3w
EP	Cisplatin (75-80 mg/m^2) or carboplatin (AUC 5-6 [For PS2 patients a dose of AUC 4 is allowed]) on Day 1 with etoposide (80-100 mg/m^2) daily on Days 1, 2 and 3	IV	Per local practice	Up to 4 to 6 cycles q3w [a]

[a] The schedule of durvalumab will be q3w while on etoposide.

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q3w until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg.

AUC: area under the curve; EP: platinum (cisplatin or carboplatin) plus etoposide; IV: intravenous; PS: performance status; q3w: every 3 weeks.

Table 7 Dose and treatment regimens post chemotherapy

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 min	q4w to PD [a]

[a] Patients are treated until PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg.

IV: intravenous; PD: progression of disease; q4w: every 4 weeks.

Table 8 Dosing schedule

	During Chemotherapy Q3W Cycles*						After Chemotherapy Q4W Cycles		
4 Cycles of D+EP schedule	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	→		Week 12	Week 16	Week 20 to PD
	EP + Durva	EP + Durva	EP + Durva	EP + Durva			Durva	Durva	Durva
5 Cycles of D+EP schedule	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Cycle 5 Week 12	→	Week 15	Week 19	Week 23 to PD
	EP + Durva	EP + Durva	EP + Durva	EP + Durva	EP + Durva		Durva	Durva	Durva
6 Cycles of D+EP schedule	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Cycle 5 Week 12	Cycle 6 Week 15	Week 18	Week 22	Week 26 to PD
	EP + Durva	EP + Durva	EP + Durva	EP + Durva	EP + Durva	EP + Durva	Durva	Durva	Durva

*EP can be given for up to 4-6 cycles if clinically indicated, based on investigator discretion. Timing of the administration of cycles is shown above for each scenario. Prophylactic cranial irradiation (PCI) can also be given at investigator discretion. This does not alter the planned scan schedule Q8W starting at Week 12 for patients.

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

Note: Patients whose weight falls to 30 kg or below must receive weight-based dosing – equivalent to 20 mg/kg of durvalumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500mg, EP= Etoposide and platinum-based chemotherapy; Durva = Durvalumab

6.1.3 Duration of Treatment and Criteria for Treatment through Progression and for Retreatment

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

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and patient as long as they are deemed to be receiving clinical benefit. A follow-up scan is to be collected after the initial RECIST 1.1-defined PD, 4-8 weeks after the prior assessment of PD; this follow-up scan is evaluated using the post-progression evaluation criteria outlined in Appendix F. Image acquisitions and tumor assessments should continue on their regular imaging schedule for the duration of treatment.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, 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 must 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 PS 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 (see Sections 5.1 and 5.2) with the exception of inclusion criteria 9.

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

At the time of the final DCO, the analysis portion of the clinical study will have been completed and all patients remaining in the study will be considered to have completed the analysis portion of the study. At the time of final DCO, the clinical study database will be closed to new data.

Patients in OS follow-up (progressed and have discontinued treatment) will be considered to have completed the study.

All patients will receive efficacy scans and follow-up care in accordance with standard local clinical practice. Data should be recorded on patient charts but will not otherwise be reported for the purposes of this study.

For patients who are continuing to receive treatment with durvalumab 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 Annex to the Protocol).

Following the DCO, SAE reporting applies only to patients who are active on IMP and within 90 days after the last dose; in all other cases, only a Statement of Death notification is to be sent to AstraZeneca.

Investigators will report SAEs to AstraZeneca Patient Safety via paper case report forms (CRFs) until 90 days after the last dose of study drug, in accordance with Section 8.4.1. Any SAE or non-serious AE ongoing at the time of the DCO is to be followed up at the discretion of the Investigator and per local practice and in alignment with the Dosing Modification and Toxicity Management Guidelines (See Annex to the Protocol), unless the event is considered by the

Investigator to be unlikely to resolve, or the patient is lost to follow-up. Data will not be captured for the purposes of this study outside of being recorded in the patients' source documents.

Different drug supply options will be available depending on the country, 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 include the participation in a new rollover study or, if the study drug has been locally approved for use in this disease indication, patients may be discontinued and switched to the marketed product, in accordance with local laws. In the event that a rollover or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new ICF.

6.1.4 Storage

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

6.2 Measures to Minimize Bias: Randomization and Blinding

6.2.1 Patient Enrollment and Randomization

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. Withdrawn patients will not be replaced.

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 be obtained within 28 days prior to first dose of IMP (see Table 1). For patients with a single TL, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired. (Informed consent of study procedures may be obtained prior to the 28-day screening window in order to permit tumor biopsy sample acquisition).

- Obtain a unique 7-digit enrollment number (E-code), through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic CRFs (eCRFs).
- Determine patient eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional).

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

Patients will begin treatment on Day 1. A window of up to 3 days is permitted between last screening assessments and first dose of IMP. Last assessments on Friday and dosing on Monday will be accepted. Patients must not be treated unless all eligibility criteria have been met.

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 incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented and that the potential benefit:risk profile remains positive for the patient.

6.3 Treatment Compliance

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

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

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 concomitant treatment, procedure, other medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the participant receives from the time of screening until the end of the clinical treatment phase of the study (including the

90-day follow-up period after the last dose of study treatment) must be recorded in the eCRF 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 supportive medications/therapies are described in Table 17, Table 18, and Table 19 of Appendix H. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.4 and Annex to Protocol).

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

6.4.1 Background Medication

Not applicable.

6.4.2 Other Concomitant Treatment

Other medications 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 CRF.

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 mAb 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 PK drug-drug interactions. The MOA 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). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for

management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the pharmacist and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the pharmacist.

6.5 Dose Modification

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

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

6.6 Treatment 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 6.1.3).

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of Study Treatment

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

- Withdrawal of consent from further treatment with IMP. 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 8.4.4 and Annex to the Protocol) or as defined in the local prescribing information for EP.
- 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 IMP (eg, refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including another investigational agent.

- Clinical progression or confirmed radiological progression (refer to Appendix F) and Investigator determination that the patient is no longer benefiting from treatment with IMP.

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

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.)

7.3 Withdrawal from the Study

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

Patients who withdraw consent for further participation in the study will not receive any further IMP 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 (Table 1 and Table 2).

The Investigator will ensure that data are recorded on the eCRFs. The Web Based Data Capture system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, 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 eCRFs. A copy of the completed eCRFs 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 (Table 1 and Table 2), 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.

8.1 Efficacy Assessments

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

Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands), collected during screening/baseline and at regular (follow-up) intervals during study treatment. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Treatment continues until clinical progression/deterioration or confirmed radiological progression (refer to Appendix F), 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 (Appendix F) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and Non-Target Lesions (NTLs). On-study images are evaluated for TLs and NTLs chosen at baseline, and for New Lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall timepoint responses (CR, PR, stable disease, PD, or Not Evaluable [NE]).

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

8.1.1 Survival Assessments

Assessments for survival must be made as shown in Table 2. 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, if available, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the DCO for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the DCO. If patients are confirmed to be alive or if the death date is after the DCO date, then these patients will be censored at the date of DCO.

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

8.1.2 CCI

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(see Appendix G).

8.1.2.2 CCI

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8.1.2.3 CCI

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8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.2.1 Clinical Safety Laboratory Assessments

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

The laboratory variables to be measured are presented in Table 9 (clinical chemistry), Table 10 (hematology), and Table 11 (urinalysis).

Other safety tests to be performed at screening include assessment for HBsAg, HCV antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Table 9 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 [d]
Chloride [c]	T3 free [e] (reflex)
Creatinine	T4 free [e] (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] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

[e] 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; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone.

Table 10 Hematology

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

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

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.

Table 11 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

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

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

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IMP 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.

8.2.2 Physical 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.

8.2.3 Vital 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 infusion day, patients will be monitored and vital signs collected/recorded in eCRF prior to, during, and after infusion of IMP as presented in the bulleted list below.

Blood pressure, pulse, temperature, and respiration rate will be collected from patients before, during, and after the first infusion at the following times (based on a 60 minute ± 10 minutes 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 ± 10 minutes)

If the infusion takes longer than 60 minutes, then BP, pulse, temperature, and respiration rate 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. Infusion of chemotherapy agents per local practice.

Subsequent Infusions

Blood pressure, 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. 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 for subsequent cycles. 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.

8.2.4 Electrocardiograms

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

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

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

8.2.5 Early Patient Review for Safety

For the first 3 cycles, patients should be contacted 1 week (±1 day) after receiving the IMP to ensure early identification and management of toxicities. This contact should be documented in the medical records.

8.2.6 WHO/ECOG Performance Status

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

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

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

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

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

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

5 Dead

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

8.2.7 Other Safety Assessments

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

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 8.4.4) 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.
- SpO_2
  - 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: C-reactive protein, lactate dehydrogenase

8.3 Collection 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.

8.3.1 Method 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.

8.3.2 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from the time of the patient signing the ICF until the follow-up period is completed (90 days after the last dose of durvalumab).

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

All 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 AEs or SAEs 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.

8.3.3 Follow-up of AEs and SAEs

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

Any AEs that are unresolved at the patient’s last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse Event Data Collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

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

It is important to distinguish between SAEs 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 it is not an 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 it would be an SAE if it satisfies the criteria shown in Appendix B 2.

8.3.5 Causality Collection

The Investigator will assess causal relationship between Investigational Product and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs, causal relationship will also be assessed for other 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: “Have you had any health problems since the previous visit/you were last asked?”, or revealed by observation will be collected and recorded in the 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 clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values 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 IMP.

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 8.3.10.

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 ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.9 Disease under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of 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 IMP.

8.3.10 Disease Progression

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

8.3.11 New Cancers

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

8.3.12 Deaths

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

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

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started 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.

8.3.13 Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IMP.

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 imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

Adverse events of special interest / 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 IBs. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.4). 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.

8.3.14 Safety Data to be Collected Following the Final DCO of the Study

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.4). 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) post the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety Reporting and Medical Management

8.4.1 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IMP, 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 AEs 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).

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

8.4.2 Overdose

8.4.2.1 Durvalumab

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

- An overdose with associated AEs 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.

8.4.2.2 Platinum and Etoposide

Use of platinum (cisplatin or carboplatin) or etoposide 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 with etoposide, cisplatin or carboplatin. If any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules in the eCRF.

8.4.3 Medication Error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-

Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

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

8.4.4 Management of IMP-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 IMP 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, or version 5.0.

8.4.4.1 Specific Toxicity Management and Dose Modification Information – Durvalumab

Comprehensive toxicity management guidelines have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint 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 (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen.

The toxicity management guidelines provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment (platinum and etoposide). The most current version of the toxicity management guidelines entitled “Dosing

Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy or in Combination with other Products" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this protocol and the Dosing Modification and Toxicity Management Guidelines). Following the first dose of IMP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy regimen by the reporting Investigator.

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

8.4.4.2 Specific Toxicity Management and Dose Modification Information - Chemotherapy

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

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

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

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

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Not applicable.

8.7 CCI

8.7.1 CCI

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8.7.2 CCI

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8.7.3 CCI

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9. STATISTICAL CONSIDERATIONS

9.1 Statistical Considerations

The primary aim of the study is to assess the safety and tolerability of Durvalumab + EP in patients with ES-SCLC. All statistical analyses will be performed by AstraZeneca or its representatives.

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

9.2 Sample Size Determination

This is a safety study and no formal sample size calculation will be done. However, a total of approximately 150 patients will be treated with durvalumab with platinum (cisplatin or carboplatin) plus etoposide. A maximum of 30% of all patients treated will have ECOG performance status of 2 at baseline. Assuming a CTCAE grade ≥ 3 incidence rate of 70%, approximately 150 patients are needed to achieve a precision no wider than 7.6% around the true incidence rate (based on Clopper-Pearson exact method). In addition, assuming an imAE incidence rate of 20%, the precision will be no wider than 6.7% around the true incidence rate. An illustration of the precision around the varying incidence rates of CTCAE grade ≥ 3 or imAE are provided in Table 12.

Table 12 Precision around varying incidence of AE

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

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

9.3 Definitions of Analysis Sets

All analyses will be performed on the safety analysis set.

9.3.1 Safety Analysis Set

The Safety Analysis Set will consist of all patients who received at least 1 dose of study treatment.

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

9.4 Outcome Measures for Analyses

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

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

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

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

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

6 **AESI**: Defined as an AE of scientific and medical interest specific to understanding of the IMP. AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. 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) 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.

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

7 **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 IMP 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.

8 **PFS12**: Defined as the proportion of patients who are alive and progression free 12 months after first date of treatment.

9 **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.

10 **OS 12**: Defined as the proportion of patients who are alive 12 months after first date of treatment.

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

12 **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.

13 **DoR12**: Defined as the proportion of patients who remain in response 12 months after first documented response per RECIST1.1.

14 CCI [redacted]

9.5 Statistical Analyses

The primary analysis, for safety, will be conducted approximately 6 months after the last patient is enrolled into the study and the final statistical analysis will be conducted after the last patient has had the opportunity to be followed up for a minimum of 12 months or 60% OS maturity, whichever occurs first.

At the time of the DCO, the analysis portion of the clinical study will have been completed and all patients remaining in the study will be considered to have completed the analysis portion of the study. At the time of DCO, the clinical study database will be closed to new data. Patients in OS follow-up (progressed and have discontinued treatment) will be considered to have completed the study.

Descriptive statistics will be used for all variables. Continuous variables will be summarized by the number of observations (n), mean, SD, 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 IMP or events absent at baseline that emerge after administration of IMP, for the period extending to 90 days after the last dose of IMP. Baseline will be the last assessment of the variable under consideration prior to the first IMP dose administration.

9.5.1 Analysis of the Primary Variable

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 AEs and imAEs will be reported for patients overall and separately by ECOG Performance Status 0-1 and 2.

9.5.2 Analysis of the Secondary Variables

9.5.2.1 Safety 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 IMP 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 IMP 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 IMP) will be flagged in the data listings.

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

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 IMP 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) where RR is in seconds

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

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

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.

9.5.2.2 Efficacy Variables

Efficacy data will be reported for all patients (details will be provided in the SAP).

Progression-free Survival

The median PFS together with the corresponding 95% CIs will be reported using Kaplan-Meier product limit methods. In addition, the proportion of patients who are progression free at 12 months will be presented.

Overall Survival

The median OS together with the corresponding 95% CIs will be reported using the Kaplan-Meier product limit methods. In addition, the proportion of patients who are alive at 12 months will be reported.

Objective Response Rate

The ORR, based on Investigator assessments (following RECIST 1.1 criteria; see Appendix F), together with the corresponding 95% CIs will be reported.

Duration of Response

The DoR will be calculated for patients who achieve an objective tumor response. Median DoR and if appropriate, CIs will be used to characterize the precision of the estimate. KM estimates will be used to provide median DoR, if appropriate. Otherwise, descriptive stats will be provided. In addition, the proportion of patients remaining in response for 12 months will be reported.

9.5.2.3 CCI

CCI

9.5.2.4 Baseline Demographics and Characteristics

In addition, demographics, medical history, comorbidities, diagnosis (eg, stage and histology), treatment duration, and prior therapeutic management of SCLC will be reported. Specific details of planned analyses will be described in the SAP.

9.5.2.5 CCI

CCI

9.5.2.6 Subgroup Analysis

Summaries for endpoints of interest by subgroup will be detailed in the SAP.

9.6 Interim Analysis

No formal interim analysis is planned for this study. The primary analysis, for safety, will be conducted approximately 6 months after the last patient is enrolled into the study and the final

statistical analysis will be conducted after the last patient has had the opportunity to be followed up for a minimum of 12 months or 60% OS maturity, whichever occurs first.

9.6.1 Steering Committee

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

9.7 Data Management by AstraZeneca or Delegate

Data management will be performed by a Contract Research Organization according to the Data Management Plan.

Any data collected through third party sources will be obtained and reconciled against study data. Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process. When all data have been coded, validated, signed, and locked, clean file will be declared, and the final database will be locked.

10. REFERENCES

Alexandrov et al 2013
Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65.

Byers and Rudin 2015
Byers La, Rudin CM. Small cell lung cancer: Where do we go from here? Cancer 2015; 121:664-672

Clark and Ihde 1998
Clark R, Ihde DC. Small-cell lung cancer: treatment progress and prospects. Oncology (Williston Park) 1998;12:647–58; discussion 661-3.

Dunn et al 2004
Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

ESMO Clinical Practice Guidelines
Früh M, De Ruysscher D, Popat S, Crino L, Peters S, Felip E. Small-cell lung cancer (SCLC):ESMO Clinical Practice Guidelines for Diagnosis, treatment and follow-up. Annals of Oncology 2013;24 (Supplement 6): vi99–vi105.

Fairman et al 2014
Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of durvalumab, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumours. J Clin Oncol, 2014 ASCO Annual Meeting Abstracts;32(5s): (suppl; abstr 2602).

Foster et al 2009
Foster N, Mandrekar S, Schild S, Nelson G, Rowland K, Deming R, et al. Prognostic Factors Differ by Tumor Stage for Small Cell Lung Cancer. Cancer 2009;115(12):2721-31

Früh et al 2013
Früh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Oncol 2013;24(Suppl6):vi99–vi105

Fukuoka et al 1991
Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 1991;83:855–61.

GLOBOCAN 2018
GLOBOCAN 2018: Lung cancer, estimated incidence, mortality, and prevalence worldwide in 2018. International agency for Research on Cancer, World Health Organization: Lyon, 2018. Available from URL: http:// http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-factsheet.pdf. Accessed on 26 August 2019.

CCI [redacted]

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

Horn et al 2018
Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.

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

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Japan Lung Cancer Society, 2018
Japan Lung Cancer Society. Lung cancer practice guidelines 2018 version III. Small cell lung cancer (SCLC). Available at: https://www.haigan.gr.jp/guideline/2018/1/3/180103020100.html (last accessed August 2, 2019).

Keir et al 2008
Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferonalpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet 2013;52:1017–27.

National Comprehensive Cancer Network 2019
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Small Cell Lung Cancer. Version 2.2020 – November 15, 2019.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Okazaki and Honjo 2007
Okazaki T and Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19(7):813-24.

Okudaira et al 2009
Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an antitumor effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Oronsky et al 2017
Oronsky B, Reid TR, Oronsky A, Carter CA. What's new in SCLC? A review. Neoplasia 2017;19:842–7.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Paz-Ares et al 2019
Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929–39.

Peifer et al 2012
Peifer M, Ferneandes-Cuesta L, Sos ML, Seidel D, Kasper LH, Plenker D, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet 2012;44(10):1104-10.

CCI [redacted]

Pietanza et al 2015
Pietanza MC, Averett Byers A, Minna JD, Rudin CM. Small cell lung cancer: will recent progress lead to improved outcomes? Clin Cancer Res 2015;21:2244–55.

Powles et al 2014
Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515(7528):558-62.

Qin et al 2016
Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016;9:2169–70.

Reck et al. 2016
Reck M, Luft A, Szczęsna A, Havel L, Kim S-W, Akerley W, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016;34(31):3740-3748.

Rizvi et al 2015
Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

Rossi et al 2012
Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 2012;30:1692-98.

Rudin et al 2015
Rudin CM, Ismaila N, Hann CL, et al. Treatment of small-cell lung cancer: American Society of Clinical Oncology endorsement of the American College of Chest Physicians guideline. J Clin Oncol 2015;33:4106–11.

Rudin et al 2020
Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double Blind, Phase III KEYNOTE-604 Study. J Clin Oncol 2020;38.

Salgia and Skarin 1998
Salgia R, Skarin AT. Molecular abnormalities in lung cancer. J Clin Oncol 1998;16(3):1207-17.

Segal et al 2015
Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

Slotman et al 2015
Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoraci radiotherapy for extensive stage small-cell lung cancer; a phase 3 randomised controlled trial. Lancet 2015;345:36-2.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3(9):1052-62.

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

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Wang et al 2017
Wang S, Tang J, Sun T, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. Sci Rep 2017;7:1339.

Zhang et al 2008
Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Antitumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy 2008;10(7):711-9.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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 International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

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

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

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.

Regulatory Reporting Requirements for Serious Adverse Events

- 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, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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 and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, 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.

Patients who are rescreened will reconfirm their consent to participate in the study by re-signing and dating their original consent form(s), next to their initial signature and date.

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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.

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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 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 ongoing 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 and 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 15 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. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. 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 multi-center 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.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

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

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

- Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, 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 NCI 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 patient or has the potential to cause harm to the patient.

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

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were 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 patient)
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the fridge when it should be at room temperature)

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

- Patient accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AZ product

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

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Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 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.

Specific guidance on managing liver abnormalities can be found in sections 8.2.1 and 8.3.8 of the Clinical Study Protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a 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 total bilirubin (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 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.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × Upper Limit of Normal (ULN) **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

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

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

E 3 Identification of Potential Hy's Law Cases

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

ALT ≥ 3 × ULN

AST ≥ 3 × ULN

TBL ≥ 2 × ULN

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 E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 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.

E 4.2 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 E)

Notify the AstraZeneca representative who will then inform the central Study Team

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol (CSP) process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change # in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the three Liver CRF Modules as information becomes available

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.

E 5 Review and Assessment of Potential Hy's Law Cases

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

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 PHL 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.

E 6 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 Appendix E

E 7 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 eg, 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 E 6 of this Appendix?

If **No**: follow the process described in Appendix E 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 E 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.

E 8 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 F 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 13.

Table 13 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: 18F-fluoro-deoxyglucose positron emission tomography/CT; MRI: magnetic resonance imaging.

CT/MRI at baseline should consider brain scan due to very common involvement of central nervous system; further CT/MRI evaluations should be according to the schedule and brain scan when clinically indicated. Additional radiological procedures such as PET/CT, bone scintigraphy and other X-rays (should be applied for non-RECIST assessments) when clinically indicated (not mandatory).

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;]), 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. 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

18F-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 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.

[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.

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

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

  - 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]
- 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.

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

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.

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:
  - TL 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 TL.

- If an Intervention on a TL 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 TL.

- 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 14 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	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; 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 or progressive disease of target disease will therefore be extremely rare.

Table 15 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 16.

Table 16 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

Target Lesions	Non-Target Lesions	New Lesions	Overall visit response
PR	Non PD or NE or NA	No	PR
Stable disease	Non PD or NE or NA	No	Stable disease
NA	Non-CR/Non-PD	No	Stable disease (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; 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, 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: no evidence of disease (NED; 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:

- $\geq$ 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 $\geq$ 5 mm in the sum of diameters at the follow-up scan timepoint compared with the immediate prior timepoint

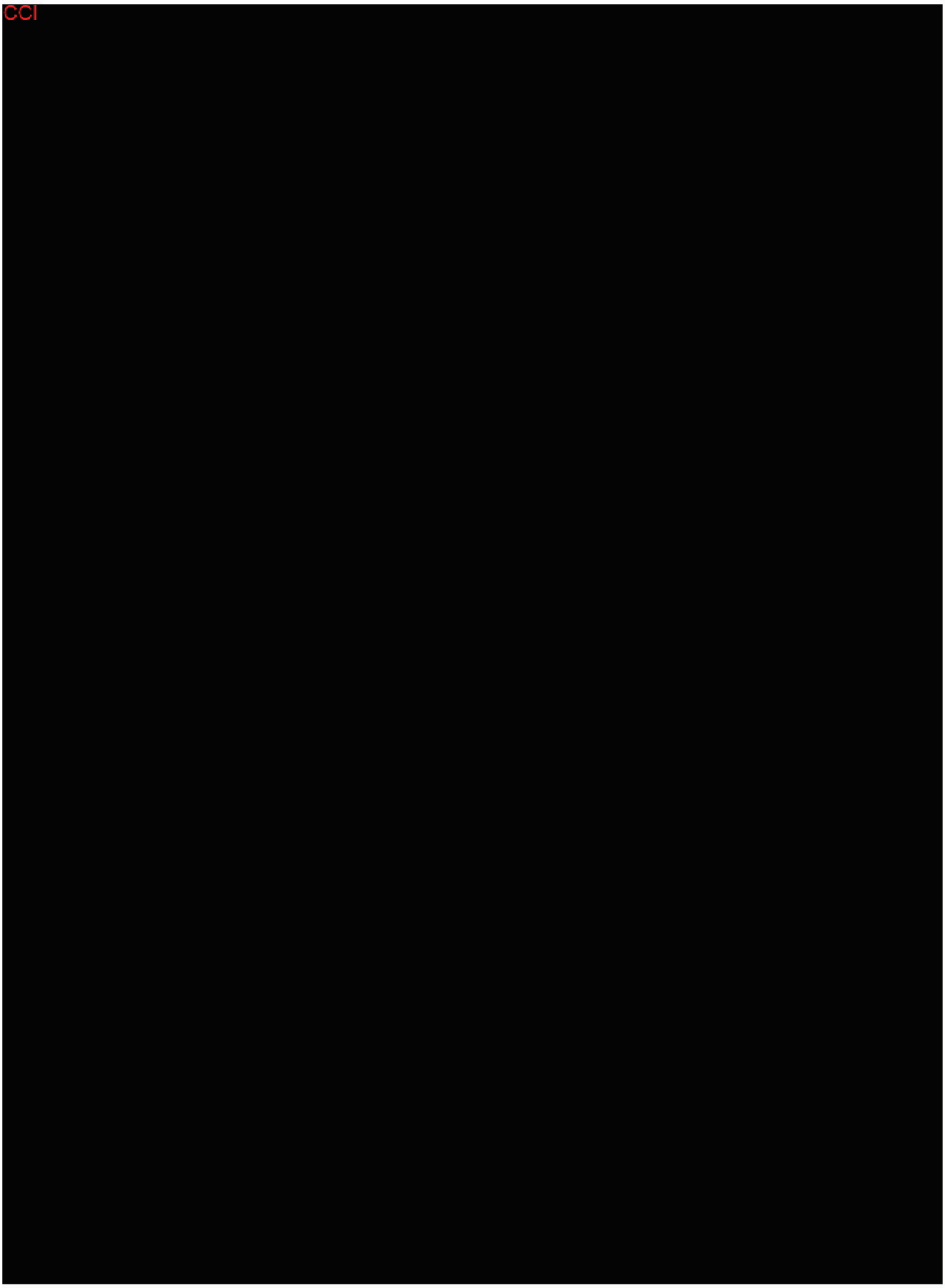
- significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of previously new lesions (pre-existing new lesions) at the follow-up scan timepoint compared with the immediate prior timepoint
- additional brand-new unequivocal lesions at the follow-up scan timepoint

References

Eisenhauer 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 G CCI

CCI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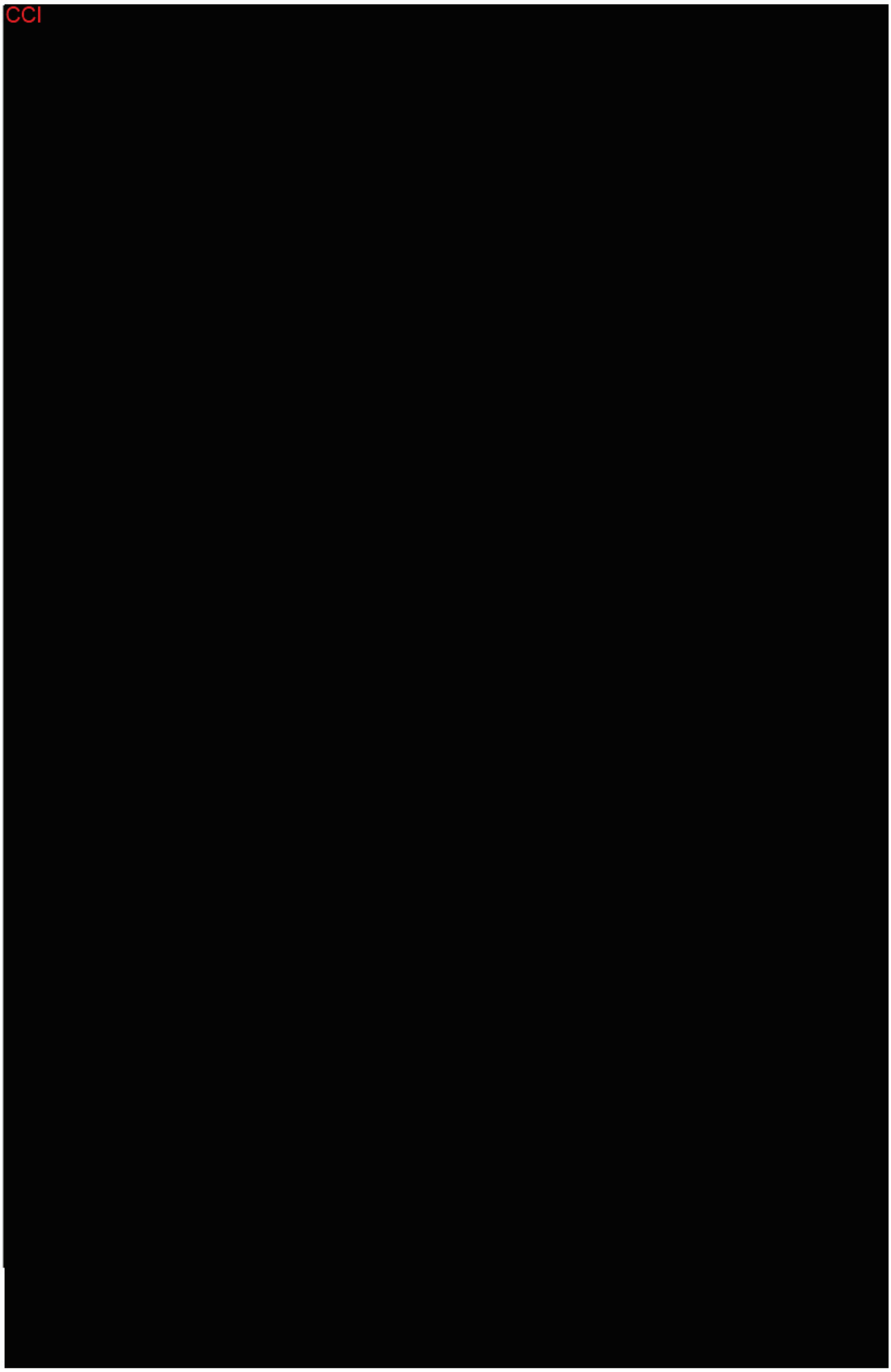
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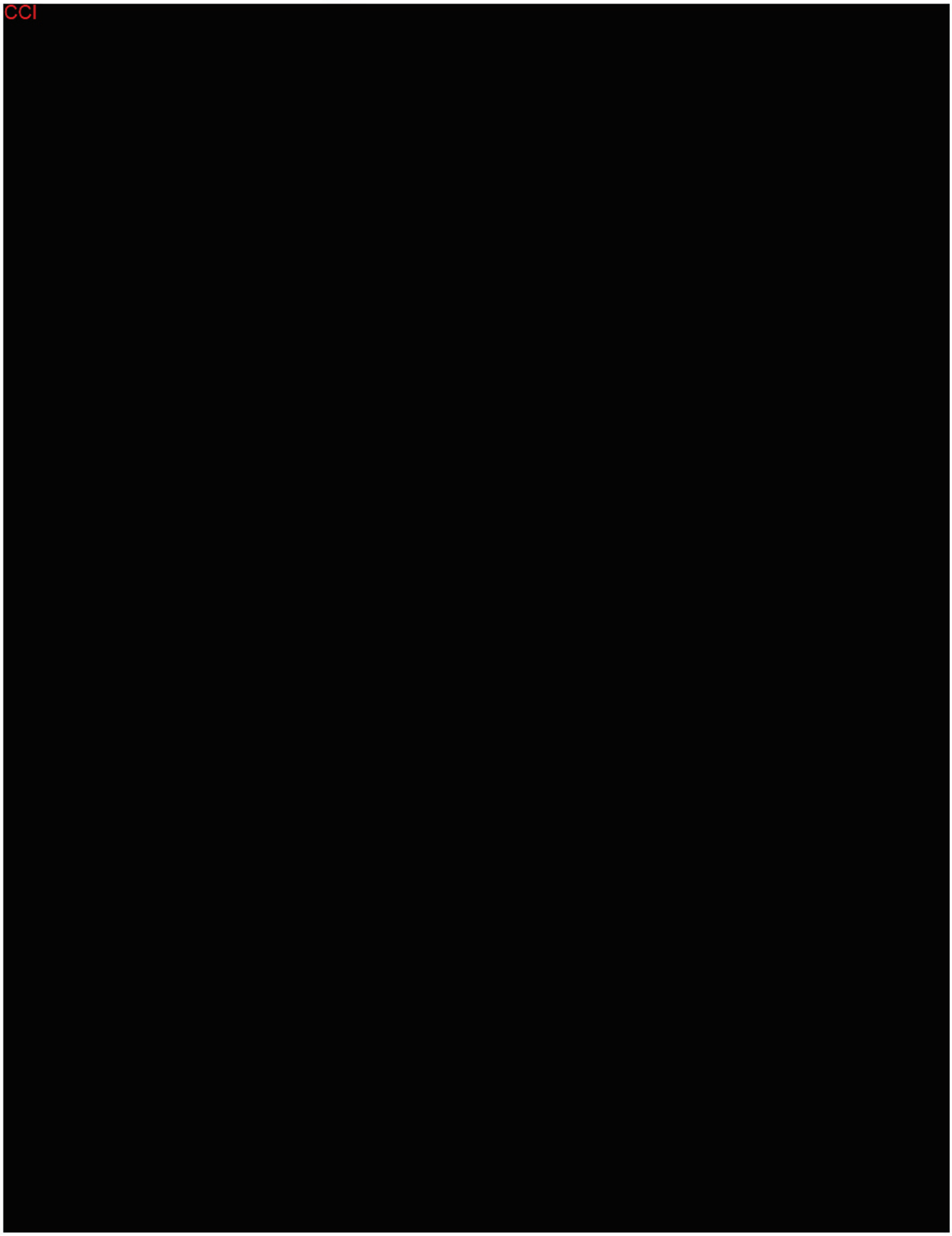
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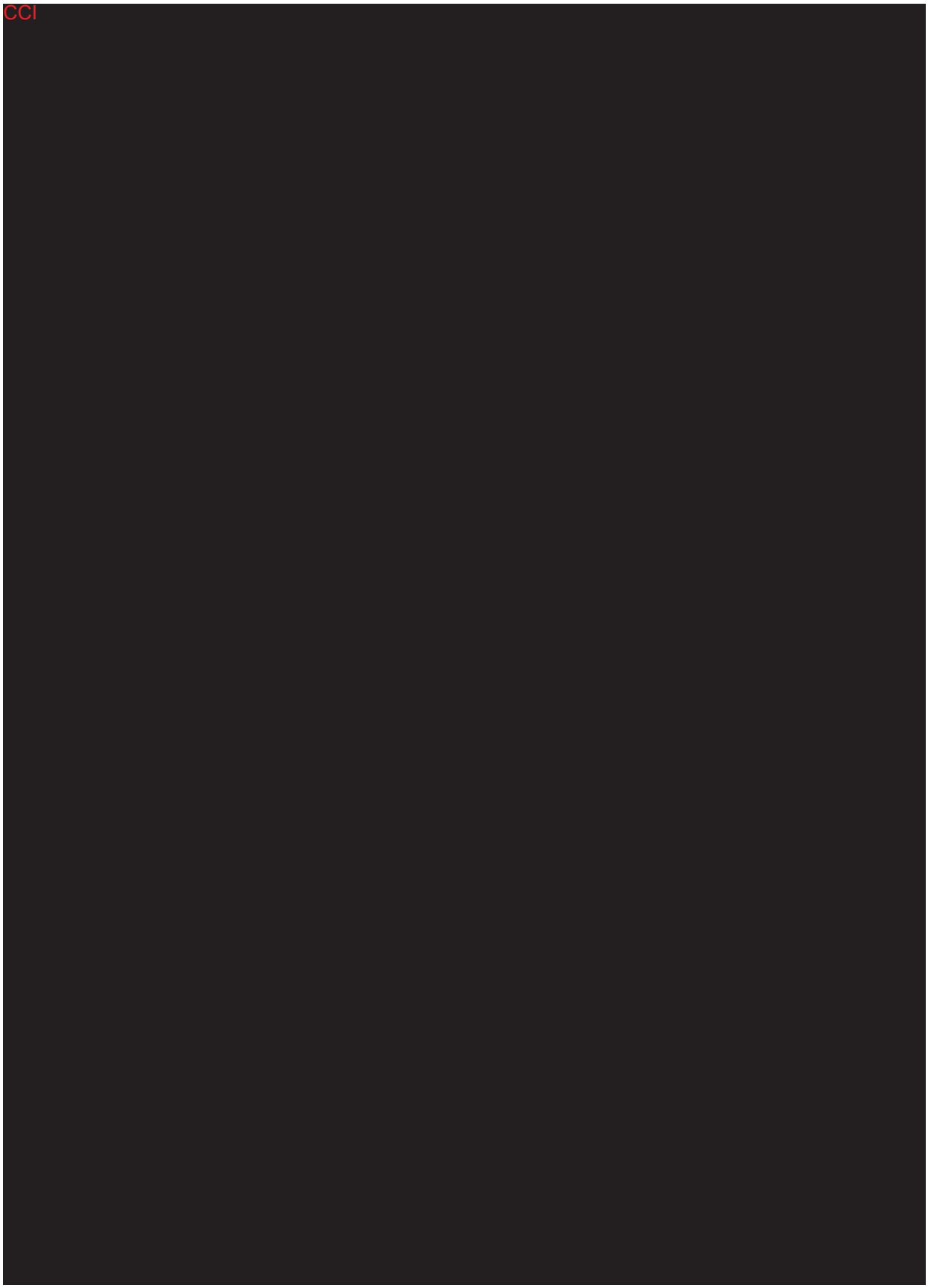
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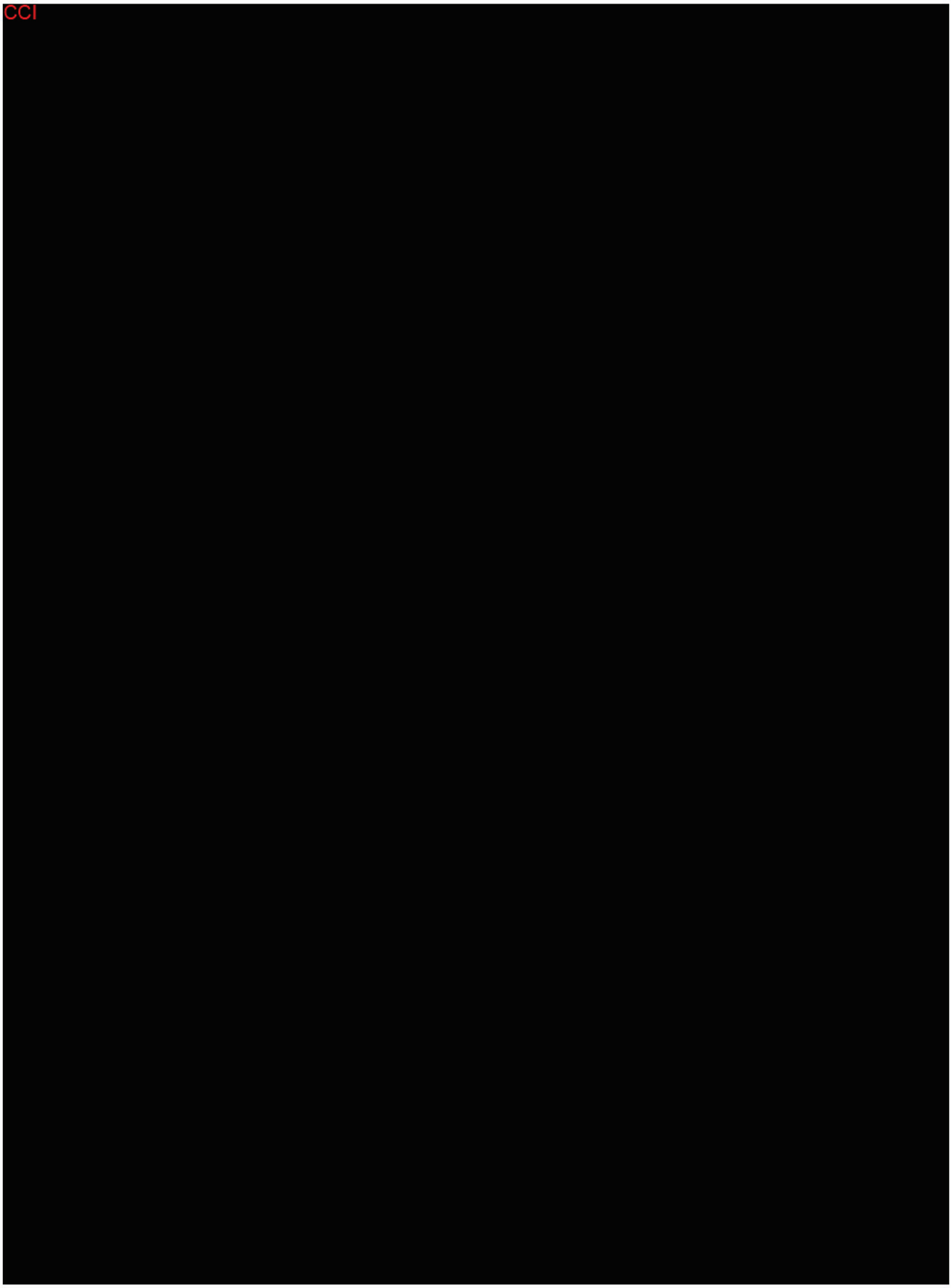

Appendix H Concomitant Medications

H 1 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and supportive medications/therapies are described in Table 17, Table 18, and Table 19. Refer also to the dose modification guidelines for management of study drug related toxicities in the Annex document to this protocol.

Table 17 Restricted Medications/Therapies

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which the drug/therapy is allowed)
Hormonal therapy	For non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) only.
Bisphosphonates	For the treatment of bone metastases and osteoporosis.
Corticosteroids	For the treatment of specific adverse drug reactions (refer to Toxicity Management Guidelines document).
Natural/herbal products, "folk remedies", vitamins, nutritional supplements	The use of these products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

Table 18 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Any investigational anticancer therapy other than those under investigation in this study	Must not be given concomitantly while the patient is on study drug.
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Must not be given concomitantly while the patient is on study drug.
Any concurrent treatment, including chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study, except for those medications identified as "restricted," as listed above	Must not be given concomitantly whilst the patient is on study drug. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Prophylactic cranial irradiation is permitted per local practice at the discretion of the treating investigator.
Live attenuated vaccines	Must not be given while receiving study treatment and up to 90 days after the last dose of durvalumab and 90 days after the last dose of etoposide. However, local guidance should be consulted to determine the acceptable timeframe for vaccine administration following chemotherapy study treatment.
Herbal and natural remedies that may have immune-modulating effects and interfere with interpretation of study results	Must not be given concomitantly unless agreed by the sponsor.

Table 18 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Must not be given concomitantly, or used for premedication prior to the IO infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study intervention-related AEs. • Short-term premedication for participants receiving combination therapy where use of a steroid is indicated to prevent a hypersensitivity or infusion reaction, or where a steroid is used as an anti-emetic. If used, it should be administered prior to chemotherapy and not prior to the IO infusion. • 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). Consult with study clinical lead for prolonged therapy or need for a slow taper.
EGFR TKIs	Must not be given concomitantly. Must 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 first generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

AE: adverse event; CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; CYP3A4/5: cytochrome P450 3A4/5; EGFR: epidermal growth factor receptor; IO: immune-oncology; PD-1: programmed cell death protein-1; PD L1: programmed death-ligand 1; TKI: tyrosine kinase inhibitor

Table 19 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate adverse event management, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 18.

Table 19 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all patients except for those medications identified as "prohibited," as listed in Table 18.
Vaccines limited only to non-live attenuated preparations (eg, influenza vaccine)	Permitted.
Natural/herbal products and "folk remedies"	Except for those medications identified as "prohibited," as listed in Table 18, the use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

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

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

I 1 Reconsent of Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections I 2 to I 5. Local and regional regulations and/or guidelines regarding reconsent of patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

I 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The investigator should confirm this with the designated study clinical lead.

In addition, during study disruption there may be a delay between confirming eligibility of a patients and either enrolment into the study or commencing of dosing with study treatment. If this delay is outside the screening window specified in Section 1.1 the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5.4. The procedures detailed in Section 6.2 must be undertaken to confirm eligibility.

I 3 Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site or TPV service may visit the patients at a remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

I 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow AEs, concomitant medication, and other relevant informationto be reported and documented.

I 5 Data Capture During Telemedicine or Remote Visits

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

I 6 COVID-19 Risk Assessment

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

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Patients enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to patients receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section I 9). With these measures in place, it is considered that the anticipated potential benefits for the patients enrolled in this study outweigh the potential risks. All implemented measures prioritise trial patient safety and data validity; in case these two conflict with each other, trial patient safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, patients with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment.

I 7 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section I 10 provides a dose modification and management plan for patients with confirmed or suspected COVID-19 who are being treated with study drug durvalumab. The risk-benefit assessment should be carefully considered for each patient enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for patients and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

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

I 8 New Patient Enrolment

Study sites may continue to recruit new patients into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new patients effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criteria 7, patients with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such patients (including those who have confirmed COVID-19) should not be included for study participation.

I 9 Study Treatment Administration

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

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

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

I 10 Ongoing Patients

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

I 10.1 If a Patient has an Event Suspected to be COVID-19

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

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the Toxicity Management Guidelines for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a patient.
- If COVID-19 is ruled out, study treatment may be resumed per the CSP.

- If COVID-19 is confirmed or diagnosis still suspected after evaluation, manage COVID-19 per local guidance until full recovery.

I 10.2 Patients with Confirmed COVID-19

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

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

I 10.3 Restarting Study Treatment

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

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

I 10.4 Vaccination Against COVID-19

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

I 11 References

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

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

Appendix J **Abbreviations**

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
CI	Confidence interval
CCI	CCI
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form (electronic/paper)
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte associated antigen 4
DCO	Data cut-off
DILI	Drug-induced liver injury
DoR	Duration of Response
DoR12	Proportion of patients remaining in response 12 months from the time of first documented objective response
EC	Etoposide/carboplatin
EC	Ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CCI	CCI
CCI	CCI
EP	Platinum (cisplatin or carboplatin) plus etoposide

Abbreviation or special term	Explanation
CCI	CCI
ES	Extensive stage
ES-SCLC	Extensive-stage small-cell lung cancer
FDA	Food and Drug Administration
FDG	Fluoro-deoxyglucose
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Hazard ratio
HRCT	High-resolution computed tomography
CCI	CCI
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
imAE	Immune mediated adverse event
IMP	Investigational medicinal product
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
IMP	Investigational medicinal product
IRB	Institutional review board
IV	Intravenous

Abbreviation or special term	Explanation
IVRS	Interactive voice response system
IWRS	Interactive web response system
LFT	Liver function test
LS	Limited stage
mAb	Monoclonal antibody
MOA	Mechanism of action
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not evaluable
NCI	National Cancer Institute
NED	No evidence of disease
NL	New lesion
NSCLC	Non-small-cell lung cancer
NTL	Non-target lesion
ORR	Overall response rate
OS	Overall survival
OS12	Proportion of patients alive at 12 months from first date of treatment
PCI	Prophylactic cranial irradiation
PD	Progression of disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PET	Positron emission tomography
PFS	Progression-free survival
PFS12	Proportion of patients alive and progression-free at 12 months from first date of treatment
PHL	Potential Hy's Law
PK	Pharmacokinetic
PR	Partial response
CCI	CCI
PS	Performance status
QTcF	Corrected QT interval using Fridericia's formulae
qXw	Every X weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Steering Committee
SCLC	Small-cell lung cancer
SD	Standard deviation
SoA	Schedule of activities
T3	Triiodothyronine
T4	Thyroxine
TBL	Total bilirubin
TL	Target lesion
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WHO	World Health Organization
WT	Weight

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