Clinical Study Protocol	
Study Intervention	AZD2811 + durvalumab
Study Code	D6132C00001
Version	9.0
Date	21 April 2022

A Phase II Multicenter, Open-Label, Single Arm Study to Determine the Efficacy, Safety and Tolerability of AZD2811 and Durvalumab Combination as Maintenance Therapy After Induction with Platinum-Based Chemotherapy Combined with Durvalumab, for the First-Line Treatment of Patients with Extensive Stage Small-Cell Lung Cancer

Sponsor Name:

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number: EudraCT Number 2020-004091-18, IND Number 152711

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 Number: D6132C00001

Amendment Number: 8
Study Intervention: AZD2811 + durvalumab
Study Phase: 2

Short Title: Phase II maintenance study of AZD2811 + durvalumab in ES-SCLC.

Study Physician Name and Contact Information will be provided separately

International co-ordinating investigator

PPD

Houston,
Texas, USA.

VERSION HISTORY

Version 9, 30 March 2022 (Amendment 8)

- Introduced global changes to align with the the decision to terminate enrolment for this study prior to completion due to the evolving benefit risk profile of AZD2811 that does not support further development for the first-line treatment of patients with extensive stage small-cell lung cancer. Patients already enrolled in the study were able to continue. However, no further patients were permitted to start AZD2811 treatment and ongoing patients transitioning into the maintenance phase in the future were offered durvalumab monotherapy. As a result of the early termination, the data cut-off for the final analysis in this study is planned for 18 June 2022.
- Sections from CSP v8.0 are retained throughout this protocol for reference. Clinical Study Protocol v8.0 was prepared to include urgent safety measures via a Dear Investigator Letter; however, CSP V 8.0 was not implemented due to early termination. Clinical Study Protocol v8.0 is superseded by CSP v9.0.
- Global change – blood samples for CCI [redacted] were reverted back to timepoints indicated in the previously approved CSP.
- Global change – The abbreviated CSR will focus on reporting safety endpoints as there were too few patients who received AZD2811 in combination with durvalumab (9 patients) to give meaningful analyses. The efficacy analyses will be streamlined and this will be fully documented in the SAP.
- Table 2 and Table 4 – Addition of +/- 1 week to the Follow-up visit.
- Section 9.4.6 – CCI [redacted]
- Administrative changes for clarity and consistency throughout.

Version 8, 10 December 2021 (Amendment 7)

- Introduced global changes to align with the Dear Investigator Letter, dated 11 October 2021.
- Administrative changes for clarity and consistency throughout.
- Global change- Changed maximum starting dose of AZD2811 in the Maintenance Phase to CCI [redacted] (previously CCI [redacted]) and added that the study aims to achieve 80 evaluable participants on the starting dose of CCI [redacted].

- Global change- Added that if short-acting G-CSF is used, it should be administered daily until at least CCI of each cycle and until the ANC has recovered to $\geq 1.5 \times 10^9$/L.
- Global change- Clarified that where possible, every effort should be made to schedule the scan within 1 week prior to dosing with AZD2811; scan results must be reviewed prior to dosing to confirm the absence of disease progression
- Synopsis- Updated to align with changes in main body of CSP.
- Table 1- Clarified CT scan to be performed during CCI scan, to confirm eligibility for maintenance phase.
- Table 1 and Table 3- CCI .
- Table 2- Added that an AE/SAE assessment is required every 2 months +/-1 week after the 90 day follow-up for participants not entering the maintenance phase.
- Table 3, Section 4.1.2.1, and Section 5.3- Added that eligibility criteria for the maintenance phase must be confirmed prior to dosing with AZD2811.
- Table 3 – Added mandatory assessments on Day 12 of Cycle 5 and Cycle 6: vital signs; concomitant medications; AE/SAE assessment; hematology; and blood sample for AZD2811 PK (postdose).
- Table 3- Clarified that a blood sample for durvalumab PK (predose) is not required beyond Day 1 of Cycle 7.
- Table 3- CCI
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- Table 3, Section 4.1, and Section 8.1- Clarified when RECIST v1.1 tumor assessments should be performed and that these scans must be reviewed prior to dosing of AZD2811.
- Table 3 and Section 7.1- Clarified that for participants receiving durvalumab monotherapy, only Day 1 visits and assessments must be completed.

- Table 3 and Table 5- Removed text stating 'G-CSF must be discontinued 48 hours prior to the next dose of AZD2811. Complete blood counts should be collected and reviewed on Day 8 and/or Day 15.'These details can be found in Section 6.2.4.
- Table 4- Specified that, for several samples, blood does not need to be drawn for participants who received re-treatment after relapse.
- Table 6- Updated sepsis to be an identified risk, rather than a potential risk, associated with AZD2811.
- Table 6- Updated pancreatitis and encephalitis to be identified risks, rather than potential risks, associated with durvalumab.
- Table 6- Removed non-infectious encephalitis as a potential risk for durvalumab.
- Section 4.1- Clairified that global recruitment will be complete when a minimum of 80 evaluable participants have entered the maintenance phase.
- Section 4.1.2.2- Clarified that if a DLT event is observed in the safety run-in study treatment will be paused for new participants entering the maintenance phase, while the SRC convenes.
- Section 4.1.2- Divided section into 3 subheadings: Section 4.1.2.1 Maintenance Phase Overview; Section 4.1.2.2 Safety Run-In; and Section 4.1.2.2.1 Results of the Safety Run-In
- Section 4.1.2.1- Clarified that participants with disease progression should not continue treatment with durvalumab monotherapy if there are any significant, unacceptable or irreversible toxicities.
- Section 4.1.2.2- Clarified that if transition of participants to maintenance therapy is paused, patients may receive durvalumab monotherapy during the pause and will be allowed to start AZD2811 therapy after the pause if eligibility criteria are met.
- Section 4.1.2.2.1- Added summary of the results of the safety run-in cohort and associated list of proposed protocol amendments.
- Section 4.1.2.2.1- Added list of proposed protocol amendments following the results of the Safety Run-In.
- Section 4.1.2.2.1- Added that after implementation of the proposed protocol amendments in CSP v8.0, an additional safety run-in cohort will be assessed by the SRC.
- Table 9 and Table 13- Updated SC dose of filgrastim to 0.5 MU (5 μg)/kg/day and removed IV dose.
- Section 4.1.4- Changed heading to "Definition of DLT-Evaluable Participants" from previous heading of "Definition of Evaluable Patients".
- Section 4.1.4- Corrected table number from Table 1 to Table 3.

- Section 4.3.2- Added that subsequent to the review of the safety run-in, the starting dose of AZD2811, in combination with durvalumab in the maintenance phase, has been reduced to a maximum of [redacted]
- Section 5.1 and Section 5.2- Changed headings to "Induction Phase Inclusion/Exclusion Criteria" from previous headings of "Inclusion/Exclusion Criteria".
- Section 5.3.1 and Section 5.3.2- Added inclusion and exclusion criteria for maintenance phase.
- Section 6.1.2- Clarified that following permanent discontinuation of any chemotherapy agent as a result of toxicity, participants may enter the maintenance phase after consultation with the Study Physician and if they meet the maintenance phase eligibility criteria.
- Section 6.1.3- Clarified that upon initial assessment of PD, treatment with AZD2811 must be discontinued but that treatment with durvalumab may be continued until radiological PD is confirmed.
- Section 6.2.4- Clarified when CBCs should be collected and reviewed.
- Section 6.5.1.1 and Section 8.5.1- Added that AZD2811 dosing should be delayed if there is any suspicion that a patient is suffering from an infection.
- Section 6.5.1.1- Added (prophylactic) antibiotics to list of permitted concomitant medications in patients who: are experiencing Grade 4 neutropenia; are at high risk of infection; or have a suspected infection.
- Section 6.5.2.1 and Table 15- Added that herbal supplements that strongly modulate CYP3A4 must not be used during the maintenance phase.
- Section 6.6.2- Clarified that dosing may be delayed due to an immune or a non-immune-related AE and, if delayed for reasons other than treatment-related toxicity, will resume as soon as feasible.
- Section 6.6.2- Updated the period of time the durvalumab dose may be delayed for, from 6 weeks, up to a maximum of 12 weeks from initiation of corticosteroids.
- Section 8.1- Added that an unscheduled imaging assessment should be performed if disease progression is suspected.
- Section 8.2- Added that participants who enter the Maintenance Phase on durvalumab monotherapy and subsequently receive AZD2811 in a later cycle require additional safety assessments and PK sampling.
- Section 8.2.3- Corrected sentence to 'triplicate 12-lead ECGs (about 5 minutes apart) pre- and post-AZD2811 and pre- and post-durvalumab infusion should be performed.'
- Table 17- Added footnote for CRP.

- Section 8.2.5- Added that participants will also be evaluated on CCI [redacted]
- Table 21- Clarified that if any toxicity does not resolve to Grade 1 or revert to baseline within 14 days, AZD2811 treatment must be discontinued.
- Table 21- Clarified that participants can only be dosed with AZD2811 on Day 1 of any Cycle if ANC is $\geq 1.5 \times 10^9$/L and platelet count is $\geq 75 \times 10^9$/L.
- Table 21- Clarified that AZD2811 should be held until Grade 2-3 ANC or Grade 2-3 thrombocytopenia (without bleeding or requirement for platelet transfusion) has resolved and then restarted at the same dose prior to the event.
- Section 8.6.2.2- Added wording 'will be collected' to clarify that mandatory fresh on-treatment tumor biopsies will be collected until core biopsy samples meeting the specified criteria are received.
- Section 8.6.2.6 and Section 8.6.2.10- Added additional timepoints for collection of blood samples in line with Table 3.
- Section 9.2- Changed sample sizes.
- Table 23, Section 9.4.2.1, and Section 9.4.2.2- Clarified that only patients who received CCI [redacted] AZD2811 + durvalumab on CCI [redacted] will be included in evaluation of primary and secondary endpoints.
- Appendix F4- Updated to reflect clarifications to tumor response evaluation timepoints throughout CSP.
- Appendix H2 and Section 11- Removed reference for Silva et al, 2011.

Version 7, 29 June 2021 (Amendment 6)

- Table 21-Hematologic Toxicity criteria for neutropenic dose reductions updated to align with the Phase 1 (D6130C00001) study and associated data

Version 6, 17 May 2021 (Amendment 5)

- Tables 1-5 Schedule of Activities: Updated Notes column throughout for consistency and to improve readability
- Table 1: Removed Day -21 to Day -7 window for some labs, and clarified that screening labs should be obtained the same day as initial consent, when possible
- Tables 1 and 3; Sections 8.6.2.3-8.6.2.11: Added a note for clarity that all assessments should be performed predose, unless otherwise indicated

- Tables 1 and 3: CCI [redacted]
- Tables 1, 2, 3, and 4 updated to include coagulation assessments with each safety lab visit
- Table 2: Renamed for clarity to include any participant who does not enter maintenance, and added "Survival Status/Subsequent Cancer Therapy" to the schedule of assessments.
- Tables 2 and 4: Clarified that the follow-up visit does not have to be a separate study visit; a phone call or other standard of care visit is acceptable
- Table 3: CCI [redacted]
- Table 8: Updated to match treatment windows in schedule of activities and to add windows to treatment
- Table 9: Updated to add treatment windows
- Table 15: Removed wording 'which may have immune-modulating effect' from 'Herbal and natural remedies' prohibited medications.
- Table 17: Footnote C inconsistencies corrected, additional footnotes added for clarity, and Carbon Dioxide added
- Table 18: White Blood Cell Differential tests defined for clarity
- Table 19: Added required test for urine microscopy for clarity
- Sections 1.2 and 8.6.2.2; Table 3: CCI [redacted]
- Added new Section 2.2.3 providing further rationale for the combination of AZD2811 and durvalumab
- Section 5.2, Exclusion #3: Clarified that culinary use of turmeric and curry is acceptable.
- Section 5.2, Exclusion #12: Clarified that if COVID-19 test is performed, the results should be reported
- Section 6.5: Added antibiotics taken within 90 days of Cycle 1 Day 1 will be recorded in the CRF
- Section 7.1.1: Moved criteria "only applies if no other anticancer therapy" as inclusion number 5, from paragraph below, for clarity.
- Appendices E1, E3, and E8: Language updated to remove references to central safety labs, as this study is using local labs only for safety assessments.

- Section 8.2.3: Clarification that sites may also report Bazett's Correction Formula (QTcB) if that is the local standard.
- Section 8.3.10 and Appendix B2: Updated "congenital abnormality" to "congenital anomaly" to align with new company standards
- Section 8.8.1: Language added to allow for use of paper back up for ePRO
- Section 9.4.2.3: Language clarified around missed RECIST assessments.

Version 5, 01 April 2021 (Amendment 4) – Italy Only

- Tables 2 and 4 updated to include additional pregnancy testing through 90 days post last dose
- Submitted as part of response to AIFA, and not submitted to any other Health Authority

Version 4, 23 February 2021 (Amendment 3) – Canada Only

- Section 5.2, Exclusion #1 language clarified to exclude history of immune mediated reactions like pneumonitis
- Section 5.2, Exclusion #8 language clarified to include pneumonitis as a type of interstitial lung disease
- Sections 4.1.1 Table 8, 4.1.2 Table 9, and 6.6.1 Table 16: Clarified observation time between infusions is elapsed time from the end of the first infusion to the start of the next infusion (or in maintenance the observation time after the end of durvalumab at the site)
- Submitted as part of response to Health Canada, and not submitted to any other Health Authority

Version 3, 04 November 2020 (Amendment 2)

- Section 5.1, Inclusion #2 language updated to "T3 or T4 tumor stage"
- Section 5.1, Inclusion #3 CCI [redacted]
- Section 5.2, Exclusion #18 was updated to clarify that this exclusion would not apply participants meeting re-treatment after relapse criteria

- Section 5.4 was updated to clarify that the maximum duration for rescreening, which must be complete within 7 weeks of initial consent
- Section 6.1.1 was updated to clarify that participants must be eligible to receive both durvalumab and AZD2811 to enter the maintenance phase
- Section 6.5 CCI [redacted]
- Section 8.2.4 moved language from 8.5.1 regarding holds due to ANC and platelet counts, also clarifying that Day 1 treatment may be delayed up to 14 days for a maximum cycle length of 35 days
- Section 8.5.1 was updated to clarify that Day 1 of a cycle may be delayed up to C [redacted] days, for a maximum cycle length of CCI [redacted]. It was also updated to clarify that the cycles are calibrated to have Day 1 always be the day that the patient received study treatment. Additionally, toxicity resolution language was updated state that toxicities should be resolved to Grade 1 or baseline for consistency
- Section 8.6.2.1 CCI [redacted]
- Appendix A5 was updated to change the SRC Chair from the International Coordinating Investigator to the Study Physician
- Updated randomized vs. enrolled vs. assigned to treatment language for clarity and consistency throughout
- Administrative changes for clarity and consistency throughout

Version 2, 02 November 2020 (Amendment 1) - United States Only

- Section 4.1.3 (DLT criteria) was updated to include Grade 4 anemia and any febrile neutropenia as DLTs
- Section 5.2 (Exclusion Criteria) was updated to clarify that prophylactic cranial irradiation (PCI) is allowed but must be completed before first dose of study medication
- Sections 5.2 (Exclusion Criteria) and 6.5.2.1 (Prohibited Concomitant Medication for AZD2811) were updated to exclude clinical inhibitors of BCRP during the safety run-in

• Section 8.5.2 (Specific Toxicity Management and Dose Modification Information - Durvalumab) was updated to specifically indicate that, in the US, dose modifications for durvalumab should be consistent with recommendations in the USPI.

Version 1, 01 September 2020 (Original Protocol)
Initial creation

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase II, multicenter, open-label, single arm study to determine the efficacy, safety, and tolerability of AZD2811 and durvalumab combination as maintenance therapy after induction with platinum-based chemotherapy combined with durvalumab, for the first-line treatment of patients with extensive stage small-cell lung cancer.

Short Title: Phase II maintenance study of AZD2811 + durvalumab in ES-SCLC.

On 14 December 2021, AstraZeneca took the decision to terminate enrolment for this study prior to completion due to the evolving benefit risk profile of AZD2811 that does not support further development for the first-line treatment of patients with extensive stage small-cell lung cancer. Patients already enrolled in the study were able to continue. However, no further patients were permitted to start AZD2811 treatment and ongoing patients transitioning into the maintenance phase after this date were offered durvalumab monotherapy. As a result of the early termination, the data cut-off for the final analysis in this study is planned for 18 June 2022.

Sections from CSP v8.0 are retained throughout this protocol for reference. Clinical Study Protocol v8.0 was prepared to include urgent safety measures via a Dear Investigator Letter; however, CSP V 8.0 was not implemented due to early termination. Clinical Study Protocol v8.0 is superseded by CSP v9.0.

Rationale: Despite improved efficacy in the treatment of extensive stage small-cell lung cancer (ES-SCLC) resulting from the addition of programmed cell death-ligand 1 immunotherapy to platinum-etoposide, there remains an urgent need for therapies that prolong progression-free survival and overall survival in this disease. Preliminary clinical data suggest that AZD2811 may be effective in stabilizing disease in later line SCLC patients. This trial will investigate whether a similar benefit can be demonstrated in first line SCLC patients treated with AZD2811 plus durvalumab maintenance therapy, following CCI of durvalumab plus platinum-etoposide induction therapy.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of AZD2811 + durvalumab by assessment of the proportion of participants alive and progression free at 12 months (APF12) who have not progressed during etoposide and platinum-based chemotherapy (EP)-durvalumab based induction therapy.	The proportion of participants APF12 will be defined as the Kaplan-Meier estimate of progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the investigator at local site at 12 months, in participants who enter the maintenance phase.

Objectives	Endpoints
Secondary	
To evaluate efficacy of AZD2811 + durvalumab by assessment of the proportion of participants alive at 12 months (OS12), 15 months (OS15), and 18 months (OS18), who have not progressed during EP-durvalumab based induction therapy.	The proportion of participants OS12, OS15, and OS18 will be defined as the Kaplan-Meier estimate of overall survival (OS) at 12 months, 15 months, and 18 months, respectively, in participants who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of the proportion of participants alive and progression free at 6 months (APF6) and 9 months (APF9) who have not progressed during EP-durvalumab based induction therapy.	The proportion of participants alive and progression free at APF6 and APF9 will be defined as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by the investigator at local site at 6 months and 9 months, respectively, in participants who enter the maintenance phase.
To evaluate efficacy of EP-durvalumab by assessment of objective response rate (ORR) in the induction phase.	ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed complete response (CR) or partial response (PR), by the investigator at local site per RECIST v1.1 in the induction phase (all participants).
To evaluate efficacy of AZD2811 + durvalumab by assessment of ORR in the participants who had not progressed during EP-durvalumab based induction therapy.	ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed CR or PR, by the investigator at local site per RECIST v1.1, in participants who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of PFS in participants who had not progressed during EP-durvalumab based induction therapy.	PFS is defined as time from date of first dose study intervention in the induction phase until progression per RECIST v1.1 or death due to any cause. The median Kaplan-Meier estimate in participants who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of OS in participants who had not progressed during EP-durvalumab based induction therapy.	OS is defined as time from date of first dose study intervention in the induction phase until the date of death due to any cause. The median Kaplan-Meier estimate in participants who enter the maintenance phase.
To assess the safety and tolerability profile of study intervention in small-cell lung cancer (SCLC).	Safety and tolerability will be evaluated in terms of adverse events, vital signs, physical examination, clinical chemistry, thyroid-stimulating hormone, prothrombin time /partial prothrombin time /international normalized ratio, hematology, electrocardiograms, and urinalysis, as well as treatment delays, dose reductions, and dose discontinuations.
To evaluate the pharmacokinetics of durvalumab and AZD2811.	Concentration of durvalumab, and AZD2811 and its metabolite in serum and whole blood, respectively.
To evaluate the effect of AZD2811 + durvalumab on SCLC symptoms and health-related quality of life (QoL) using European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) and 13-	EORTC QLQ-C30: Symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Health-related QoL/functioning (physical function, role function, emotional function, cognitive function, social function,

Objectives	Endpoints
item Lung Cancer Quality of Life Questionnaire (QLQ-LC13).	and global health status/QoL). EORTC QLQ-LC13: Disease-related symptoms (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and other pain).

For Exploratory objectives and endpoints, see Section 3.

Overall Design

This is a Phase II, multicenter, open-label, single arm study in ES-SCLC treatment naïve patients who do not progress per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 after induction with etoposide and platinum-based chemotherapy-durvalumab.

Participants will be treated for CCI on an everyCCI schedule in an induction phase with platinum-based induction therapy (cisplatin or carboplatin plus etoposide) + durvalumab. At the end of this induction period, participants will be assessed for disease progression, per RECIST v1.1.

Participants who have not progressed per RECIST v1.1 at the end of the induction phase will continue into the maintenance phase of the trial following confirmation of maintenance phase eligibility criteria.

The maintenance phase will commence with a safety run-in period, in which approximately six participants will be followed for (at least) one cycle, to assess safety of the AZD2811 + durvalumab combination in order to provide the earliest opportunity to assess tolerability of the combination in those approximately six participants. After the completion of ≥CCI (≥ 1 cycle) dosing in the first 6 evaluable participants, all safety data (including, but not limited to, dose-limiting toxicities, adverse events of special interest, laboratory safety assessment, vital signs, and physical examination), will be assessed to judge if the combination is safe and tolerable. This assessment, and subsequent recommendation to continue dosing in the maintenance phase, will be undertaken by a Safety Review Committee (SRC). Participants will be treated with AZD2811 + durvalumab as maintenance therapy until confirmed progressive disease, start of non-protocol defined anticancer therapy, unacceptable toxicity, or withdrawal of consent.

Disclosure Statement: This is an open-label treatment, single arm study.

Number of Participants:

Approximately 100 participants will be assigned to treatment to achieve 80 evaluable participants having received maintenance therapy.

From Clinical Study Protocol (CSP) v8.0 onwards, the starting dose of AZD2811 in the

maintenance phase will be CCI, the study will seek to achieve 80 evaluable participants on that starting dose.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered "screen failures", unless otherwise specified by the protocol. "Assigned" means that a participant has completed the screening period and has received at least one dose of study treatment.

Intervention Groups and Duration: A single group of participants will be treated as follows:

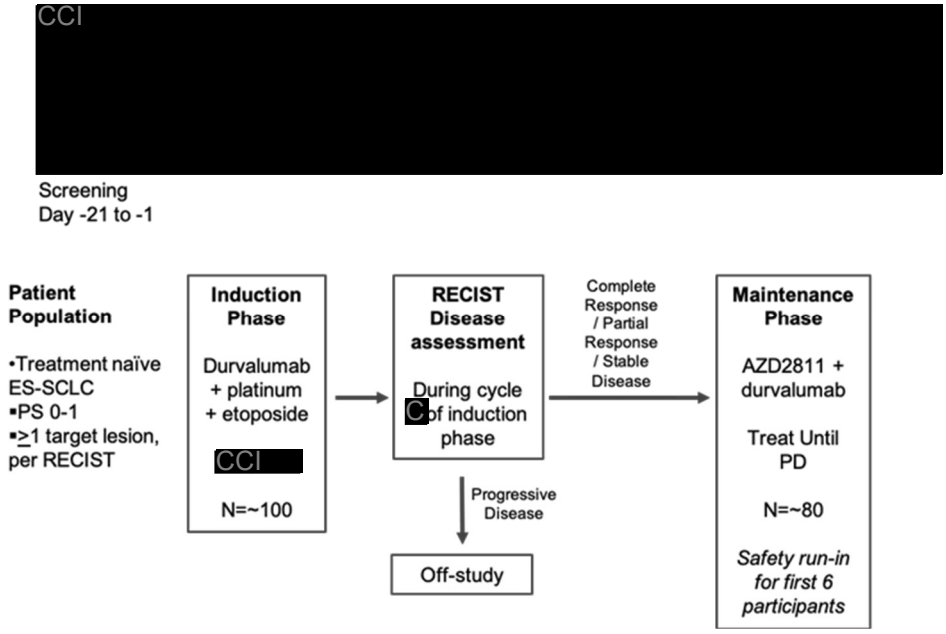
- Screening: Days -21 to Day -1
- Induction Phase: CCI to CCI
  - Durvalumab CCI
  - Carboplatin (area under the curve 5 to 6) or cisplatin (75 to 80 mg/m^2) CCI
  - Etoposide (80 to 100 mg/m^2) on CCI
- Maintenance Phase: CCI to confirmed disease progression
  - AZD2811 (CCI with mandatory granulocyte colony stimulating factor on/from CCI
  - Durvalumab (CCI)

Data Monitoring Committee: A SRC will be used to assess the participants in the safety run-in.

Statistical Methods: The study is single arm so there will be no formal statistical hypotheses. The analysis for the study will be descriptive.

1.2 Schema

Figure 1 Study Design



C = cycle; D = day; ES-SCLC = extensive stage small-cell lung cancer; PD = progressive disease; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors.

CCI

1.3 Schedule of Activities

Table 1 Schedule of Activities for the Induction Period

	Screening[a]	During Induction Chemotherapy 1 cycle = CCI																Notes	Details in CSP Section or Appendix
		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C3	C3	C4	C4	C4	C4		
Week		CCI																	
Day	**-21 to -1**																		
Window (days) unless a dose delay is needed for toxicity management	NA				± 3	± 3			± 3	± 3			± 3	± 3			± 3		
Informed consent	X																		Appendix A 3
Eligibility criteria	X	X																	Section 5.1 and 5.2
Maintenance eligibility check																	X	Confirm participant does not have progressive disease on C4 scan	
Physical examination (full)	X																		Section 8.2.1
Targeted physical examination (based on symptoms)		X				X				X				X				Skin must be assessed at each visit regardless of changes	Section 8.2.1
Vital signs	X	X[b]			X	X			X	X			X	X			X		Section 8.2.2
Triplicate 12-lead ECG	X	As clinically indicated																	Section 8.2.3

Table 1 Schedule of Activities for the Induction Period

	Screening[a]	During Induction Chemotherapy 1 cycle = CCI															Notes	Details in CSP Section or Appendix
		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C3	C3	C4	C4	C4	C4	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 6.5
CCI																			Section 6.5
Medical history and demography, including baseline characteristics, and tobacco history	X																	Collecting smoking pack-years	Section 8.2
Clinical chemistry[b, c]	X	X[b]			X	X			X	X			X	X			X	Results for urea and electrolytes, and liver function tests must be available before commencing an infusion	Section 8.2.4
Hematology [b, c]	X	X[b]			X	X			X	X			X	X			X	Results for full blood count must be available before commencing an infusion	Section 8.2.4
Fibrinogen and CRP	X									X									Section 8.2.4
TSH, free T_3, and free T_4	X	X[b]				X				X				X					Section 8.2.4
PT/PTT/INR [b, c]	X	X[b]			X	X			X	X			X	X			X		Section 8.2.4

Table 1 Schedule of Activities for the Induction Period

	Screening[a]	During Induction Chemotherapy 1 cycle = CCI															Notes	Details in CSP Section or Appendix
		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C3	C3	C4	C4	C4	C4	
		CCI																
Urinalysis [b, c]	X	X[b]				X				X				X				Section 8.2.4
spO_2 assessment	X	As clinically indicated								X							If abnormal at any time during the study, to be repeated on Day 1 of subsequent cycles.	Section 8.2.7
Hepatitis B and C and HIV	X	As clinically indicated																Section 8.2.4
Tuberculosis Test	X	As clinically indicated																Section 8.2.4
Pregnancy test	X	X[b]				X				X				X				Section 8.2.4
Tumor evaluation (CT or MRI) (RECIST 1.1) Chest /Abdomen	X								X								X	Participant's diagnostic scan may be used as a baseline scan if taken within 28 days of C1D1 and in accordance with the requirements outlined in Appendix F. CCI , for confirmation of maintenance eligibility.	Section 8.1 and Appendix F
Tumor evaluation (CT or MRI) (RECIST v1.1) Pelvis /Additional Anatomy (as	X								X								X	Performed at baseline and follow up assessments if appropriate based on signs and symptoms of the participant	Section 8.1.1

Table 1 Schedule of Activities for the Induction Period

	Screening[a]	During Induction Chemotherapy 1 cycle = CCI																Notes	Details in CSP Section or Appendix
		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C3	C3	C4	C4	C4	C4		
clinically indicated)																			
ECOG performance status	X	X			X	X				X				X					Section 8.2.6
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.3 and 8.2.7
Durvalumab		CCI																	Section 4.1 and 6.2.2
Etoposide		CCI																The immunotherapy agents are infused first followed by the etoposide (CCI) + cisplatin/carboplatin regimen. Infuse over 0.5 to 1 hour.	Section 4.1 and 6.2.3
Carboplatin or cisplatin		CCI																The immunotherapy agents are infused first followed by the etoposide + cisplatin/carboplatin (C) regimen. If cisplatin, infuse over 1 to 2 hours. If carboplatin, infuse over 0.5 to 1 hour.	Section 4.1 and 6.2.3
EORTC QLQ-C30 v3, EORTC QLQ-LC13	X	X				X				X				X				PRO should be collected prior to any other visit procedures to avoid bias in the event of PD	Section 8.8.1

Table 1 Schedule of Activities for the Induction Period

	Screening[a]	During Induction Chemotherapy 1 cycle = CCI															Notes	Details in CSP Section or Appendix
		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C3	C3	C4	C4	C4	C4	
		CCI																
CCI																		Section 8.7; Appendix D
																		Section 8.6.2.1
																		Section 8.6.2.2

Table 1 Schedule of Activities for the Induction Period

		During Induction Chemotherapy 1 cycle = CCI																	
		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C3	C3	C4	C4	C4	C4		
	Screening[a]	CCI																Notes	Details in CSP Section or Appendix
CCI																			Section 8.6.2.3
																			Section 8.6.2.4
																			Section 8.6.2.5
																			Section 8.6.2.6
																			Section 8.6.2.7
																			Section 8.6.2.8

Table 1 Schedule of Activities for the Induction Period

	Screening[a]	During Induction Chemotherapy 1 cycle = CCI															Notes	Details in CSP Section or Appendix
	CCI	C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C3	C3	C4	C4	C4	C4	
CCI																		Section 8.6.2.9
																		Section 8.6.2.10
																		Section 8.6.2.11

AE = Adverse event; C = Cycle; CCI ; CRP = C-reactive protein; CSP = Clinical study protocol; CT = Computed tomography; CCI ; D = Day; CCI ; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; HIV = Human immunodeficiency virus; INR = International normalized ratio; IV = Intravenous; MRI = Magnetic resonance imaging; NA = not applicable; CCI ; PD = Progressive disease; PRO = Patient-reported outcomes; PT = prothrombin time; PTT = partial prothrombin time; QLQ C30 v3 = 30 item Core Quality of Life Questionnaire, version 3; QLQ-LC13 = 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = Serious adverse event; SpO2 = Saturation of peripheral oxygen; T_3 = Triiodothyronine; T_4 = Thyroxine; TSH = Thyroid-stimulating hormone.

[a] Screening procedures should be performed on the same day as consent, when possible, including CCI and PRO.
[b] Assessments do not need to repeated on C1D1 if within 3 days of screening assessment.
[c] Assessments do not need to be repeated on Day 1 of a cycle if performed within 3 days of the visit.

All assessments, including exploratory and safety labs, must be performed pre-dose, unless otherwise specified.

Table 2 Schedule of Activities for the End of Treatment Period for Participants Who Do Not Enter the Maintenance Phase

Procedure	Disease Progression	EOT	FU (90 days +/-1 week after last dose)	Every 2 months+/- 1 week following FU	Notes	Details in CSP Section or Appendix
Vital signs		X				Section 8.2.2
Physical examination	X	X				Section 8.2.1
ECOG performance status		X				Section 8.2.6
Concomitant medications	X	X	X		Participant to return [redacted]/EOT	Section 6.5
AE/SAE assessment	X	X	X	X	Participants should be asked about any skin changes or rashes at each visit.	Section 8.3
Single 12-lead ECG		X				Section 8.2.3
Hematology		X				Section 8.2.4
Clinical chemistry		X				Section 8.2.4
PT/PTT/INR		X				Section 8.2.4
Fibrinogen and CRP		X				Section 8.2.4
Pregnancy test		X	X		In women of childbearing potential only. Pregnancy testing will be performed monthly (28 days +/- 7 days) through 90 days post last dose or until a new treatment is initiated, whichever is shorter. The pregnancy testing can be performed at a standard of care visit, and does not require a separate study visit.	Section 8.2.4
Survival Status/subsequent cancer therapy				X	A separate study visit is not required. Data from a standard of care visit or a phone call may be used.	Section 8.1.2

AE = Adverse event; CRP = C-reactive protein; CSP = Clinical study protocol; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of treatment; FU = Follow-up; INR = International normalized ratio; PT = prothrombin time; PTT = partial prothrombin time; SAE = Serious adverse event.

Table 3 Schedule of Activities for the Maintenance Period

Procedure	During Maintenance Phase [a] (1 cycle = CCI)													Notes	Details in CSP Section or Appendix
	Cycle 5 (cycle = CCI					Cycle 6						Cycle 7 and beyond			
	CCI														
Window (days) unless a dose delay is needed for toxicity management	**± 1**				**± 2**	**± 1**					**± 2**	**± 1**		**± 2**	
Eligibility Criteria	X														Must be confirmed prior to dosing with AZD2811	Section 5.3
Physical examination (full)	X					X						X			Skin should be examined at each visit regardless of changes	Section 8.2.1
Vital signs	X		X	X	X	X				X	X	X			Day 12 assessments are mandatory for Cycles 5 and 6; additional Day 12 visits may be conducted at the discretion of the Investigator.	Section 8.2.2
ECOG performance status	X					X						X				Section 8.2.6
Concomitant medications	X	X	X	X	X	X	X Day 2 OR Day 3		X	X	X	X	X	X		Section 6.5
CCI																Section 6.5
AE/SAE assessment	X	X	X	X	X	X	X Day 2 OR Day 3		X	X	X	X	X	X		Section 8.3 and 8.2.7
Triplicate 12-lead ECGs	X	As clinically indicated														Section 8.2.3

Table 3 Schedule of Activities for the Maintenance Period

Procedure	During Maintenance Phase [a] (1 cycle = CCI)														Notes	Details in CSP Section or Appendix
	Cycle 5 (cycle = CCI)					Cycle 6						Cycle 7 and beyond				
	CCI															
Window (days) unless a dose delay is needed for toxicity management	**± 1**				**± 2**	**± 1**					**± 2**	**± 1**		**± 2**		
Hematology	X		X	X	X	X				X	X	X		X	Day 12 assessments are mandatory for Cycles 5 and 6; additional Day 12 visits may be conducted at the discretion of the Investigator.	Section 8.2.4
Clinical chemistry	X		X		X	X					X	X		X		Section 8.2.4
Urinalysis	X					X						X				Section 8.2.4
spO2 assessment	X	As clinically indicated													To be collected if clinically indicated and at the end of therapy. If abnormal, to be repeated on Day 1 of subsequent cycles.	Section 8.2.7
PT/PTT/INR	X		X		X	X					X	X		X		Section 8.2.4
Fibrinogen and CRP	X					X						X				Section 8.2.4
TSH, free T_3, and free T_4	X					X						X				Section 8.2.4
Pregnancy test	X					X						X				Section 8.2.4
EORTC QLQ-C30 v3, EORTC QLQ-LC13	X					X						Day 1 of every other cycle, starting with cycle 8			PRO should be collected prior to any other visit procedures to avoid bias in the event of PD	Section 8.8.1

Table 3 Schedule of Activities for the Maintenance Period

Procedure	During Maintenance Phase [a] (1 cycle = CCI)													Notes	Details in CSP Section or Appendix
	Cycle 5 (cycle = CCI					Cycle 6					Cycle 7 and beyond				
	CCI														
Window (days) unless a dose delay is needed for toxicity management	**± 1**				**± 2**	**± 1**					**± 2**	**± 1**		**± 2**	
Blood sample for AZD2811 PK (Predose)	X					X									Section 8.6.1
Blood sample for AZD2811 PK (Postdose)	X	X	X	X	X	X			X	X		X Day 1 and Day 8 of Cycles 7 and 8 only			PK blood samples will be collected from all participants 2 hours (± 15 minute from the start of infusion for each time point)	Section 8.6.1
Blood sample for durvalumab PK (Predose)	X											X Day 1 of Cycle 7 only				Section 8.6.1
CCI																Section 8.6.2.2
																Section 8.6.2.3
																Section 8.6.2.4
																Section 8.6.2.5

Table 3 Schedule of Activities for the Maintenance Period

Procedure	During Maintenance Phase [a] (1 cycle = CCI)														Notes	Details in CSP Section or Appendix
	Cycle 5 (cycle = CCI)					Cycle 6						Cycle 7 and beyond				
	CCI															
Window (days) unless a dose delay is needed for toxicity management	**± 1**				**± 2**	**± 1**					**± 2**	**± 1**		**± 2**	**Notes**	**Details in CSP Section or Appendix**
CCI																Section 8.6.2.6
																Section 8.6.2.7
																Section 8.6.2.8
																Section 8.6.2.9
																Section 8.6.2.10
																Section 8.6.2.11
CT Scan or MRI Chest/Abdomen	RECIST v1.1 tumor assessments should be performed at W18, 24, 30 and 36 ± 1 week and every 8 weeks ± 1 week thereafter. The weeks are referenced to the first dose of study intervention in the induction phase.														Where possible, every effort should be made to schedule the scan within 1 week prior to dosing with AZD2811; scan results MUST be reviewed prior to dosing to confirm the absence of disease progression.	Section 8.1
CT Scan or MRI Pelvis /Additional Anatomy	As clinically indicated															Section 8.1.1

Table 3 Schedule of Activities for the Maintenance Period

Procedure	During Maintenance Phase [a] (1 cycle = CCI)														Notes	Details in CSP Section or Appendix
	Cycle 5 (cycle = CCI)					Cycle 6						Cycle 7 and beyond				
	CCI															
Window (days) unless a dose delay is needed for toxicity management	± 1				± 2	± 1					± 2	± 1		± 2		
Durvalumab administration	CCI															Section 4.1 and 6.2.2
AZD2811 administration																Section 4.1 and 6.2.1
G-CSF																Section 6.2.4

AE = Adverse event; ANC = absolute neutrophil count; C = Cycle; CBCs = complete blood counts; CCI ; CRP = C-reactive protein; CSP = Clinical study protocol; CT = Computed tomography; CCI D = Day; CCI ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; G-CSF = granulocyte colony stimulating factor; INR = international normalized ratio; IV = Intravenous; MRI = Magnetic resonance imaging; CCI ; PD = Progressive disease; PK = Pharmacokinetic(s); PRO = Patient-reported outcomes; PT = prothrombin time; PTT = partial prothrombin time; QLQ C30 v3 = 30 item Core Quality of Life Questionnaire, version 3; QLQ-LC13 = 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = Serious adverse event; SpO2 = Saturation of peripheral oxygen; T_3 = Triiodothyronine; T_4 = Thyroxine; TSH = Thyroid-stimulating hormone; W = Week.

[a] For participants starting the maintenance phase with durvalumab monotherapy, who subsequently receive AZD2811 in a later cycle (ie, beyond Cycle 5), additional safety assessments and PK sampling are required. See Section 8.2.

[b] Only if short-acting G-CSF (filgrastim) is administered.

All assessments, including [redacted] and safety labs, must be performed pre-dose, unless otherwise specified.

Table 4 Schedule of Activities for the End of Treatment Period for Participants Entering the Maintenance Phase and Re-Treatment After Relapse Participants

Procedure	Disease Progression	EOT	FU (90 days +/- 1 week after last dose)	Every 2 months+/- 1 week following FU	Notes	Details in CSP Section or Appendix
Vital signs		X				Section 8.2.2
Physical examination	X	X			Skin to be assessed at each visit regardless of changes	Section 8.2.1
ECOG performance status		X				Section 8.2.6
Concomitant medications	X	X	X		Participant to return [redacted] at Disease Progression/EOT	Section 6.5
AE/SAE assessment	X	X	X		Participants should be asked about any skin changes or rashes at each visit.	Section 8.3
Single 12-lead ECG		X				Section 8.2.3
Hematology		X				Section 8.2.4
Clinical chemistry		X				Section 8.2.4
PT/PTT/INR		X				Section 8.2.4
Fibrinogen and CRP		X				Section 8.2.4

Table 4 Schedule of Activities for the End of Treatment Period for Participants Entering the Maintenance Phase and Re-Treatment After Relapse Participants

Procedure	Disease Progression	EOT	FU (90 days +/- 1 week after last dose)	Every 2 months+/- 1 week following FU	Notes	Details in CSP Section or Appendix
Pregnancy test		X	X		In women of childbearing potential only. Pregnancy testing will be performed monthly (28 days +/- 7 days) through 90 days post last dose or until a new treatment is initiated, whichever is shorter. The pregnancy testing can be performed at a standard of care visit, and does not require a separate study visit.	Section 8.2.4
CCI [redacted]						Section 8.6.2.2
						Section 8.6.2.3
						Section 8.6.2.4
						Section 8.6.2.5
						Section 8.6.2.6
						Section 8.6.2.7
						Section 8.6.2.8
						Section 8.6.2.9

Table 4 Schedule of Activities for the End of Treatment Period for Participants Entering the Maintenance Phase and Re-Treatment After Relapse Participants

Procedure	Disease Progression	EOT	FU (90 days +/- 1 week after last dose)	Every 2 months+/- 1 week following FU	Notes	Details in CSP Section or Appendix
CCI						Section 8.6.2.10
						Section 8.6.2.11
CT Scan or MRI Chest/Abdomen	RECIST v1.1 tumor assessments should be performed at W18, 24, 30 and 36 ± 1 week and every 8 weeks ± 1 week thereafter. The weeks are referenced to the first dose of study intervention in the induction phase (Cycle 1 Day 1).				**For participants who have discontinued treatment due to safety reasons only.**	Section 8.1.1
Survival Status/subsequent cancer therapy				X	A separate study visit is not required. Data from a standard of care visit or a phone call may be used.	Section 8.1.2
Second progression assessment				X	Participants who discontinue study intervention following progression will be assessed every 8-12 weeks for a second progression (using the participant's status at first/confirmed progression as the reference for assessment of second progression). A participant's progression status is defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death (using the participant's status at first progression as the reference for assessment of second progression).	Section 8.1.1

AE = Adverse event; CCI ; CRF = case report form; CRP = C-reactive protein; CSP = Clinical study protocol; CT = Computed tomography; CCI DCO = data cut-off; CCI ; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic CRF; EOT – End of treatment; FU = Follow-up; INR = International normalized ratio; IV = Intravenous; MRI = Magnetic resonance imaging; OS = overall survival; PBMCs = peripheral blood mononuclear cells; PD = Progressive disease; PT = prothrombin time; PTT partial prothrombin time; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = Serious adverse event; SCLC = small-cell lung cancer; W = Week.

Table 5 Schedule of Activities for Re-treatment after Relapse

Procedure	Screening	Re-treatment Cycle 1 (cycle = C [redacted] C)			Re-treatment Cycle 2			Re-treatment Cycle 3		Continued	Notes	Details in CSP Section or Appendix
	Day -21 to -1	Day (± 2 D)			Day (± 2 D)			Day (± 2 D)				
		CCI [redacted]										
Window (days) unless a dose delay is needed for toxicity management	NA			± 2			± 2					
Informed consent	X											
Eligibility criteria	X											
Physical examination	X	X			X			X		CCI [redacted]	Procedures can be performed as clinically indicated/less frequently if considered appropriate by the investigator or if not required by Institutional Guidelines with a minimum at the beginning of each cycle and at the end of treatment.	Section 8.2.1
Vital signs	X	X	X	X	X		X	X		CCI [redacted]	Procedures can be performed as clinically indicated/less frequently if considered appropriate by the investigator or if not required by Institutional Guidelines with a minimum at the beginning of each cycle and at the end of treatment.	Section 8.2.2
ECOG performance status	X	X			X			X		CCI [redacted]		Section 8.2.6
Concomitant medications	X	X	X	X	X	X	X	X	X	At each visit		Section 6.5
AE/SAE assessment	X	X	X	X	X	X	X	X	X	At each visit	Participants should be asked about any skin changes or rashes at each visit. AEs and SAEs will be collected until 90 days following the last dose of study intervention.	Section 8.3 and 8.2.7

Table 5 Schedule of Activities for Re-treatment after Relapse

Procedure	Screening	Re-treatment Cycle 1 (cycle = C [redacted] C)			Re-treatment Cycle 2			Re-treatment Cycle 3		Continued	Notes	Details in CSP Section or Appendix
	Day -21 to -1	Day (± 2 D)			Day (± 2 D)			Day (± 2 D)				
		CCI [redacted]										
Window (days) unless a dose delay is needed for toxicity management	NA			± 2			± 2					
Triplicate 12-lead ECGs	X	X	As clinically indicated									Section 8.2.3
Hematology	X	X	X	X	X		X	X		CCI	Procedures can be performed as clinically indicated/less frequently if considered appropriate by the investigator or if not required by Institutional Guidelines with a minimum at the beginning of each cycle and at the end of treatment.	Section 8.2.4
Clinical chemistry	X	X	X	X	X		X	X		CCI	Procedures can be performed as clinically indicated/less frequently if considered appropriate by the investigator or if not required by Institutional Guidelines with a minimum at the beginning of each cycle and at the end of treatment.	Section 8.2.4
PT/PTT/INR	X	X	As clinically indicated									Section 8.2.4
Fibrinogen and CRP	X	X			X			X		CCI	Pre-infusion of AZD2811 in each cycle	Section 8.2.4
TSH, free T_3, and free T_4	X	X			X			X		CCI		Section 8.2.4
Pregnancy test	X	X			X			X		CCI	In women of childbearing potential only, at the beginning of each treatment cycle. Urine is acceptable.	Section 8.2.4

Table 5 Schedule of Activities for Re-treatment after Relapse

Procedure	Screening	Re-treatment Cycle 1 (cycle = C [redacted] C)	Re-treatment Cycle 2	Re-treatment Cycle 3	Continued	Notes	Details in CSP Section or Appendix
	Day -21 to -1	Day (± 2 D)	Day (± 2 D)	Day (± 2 D)			
		CCI [redacted]					
Window (days) unless a dose delay is needed for toxicity management	NA	± 2	± 2				
CT Scan or MRI Chest/Abdomen	X	RECIST v1.1 tumor assessments should be performed at RC1, and every 8 weeks ± 1 week thereafter until death, progressive disease, or the end of study)			Per Institutional Guidelines		Section 8.1.1
CT Scan or MRI Pelvis /Additional Anatomy	As clinically indicated						Section 8.1.1
Durvalumab administration	CCI [redacted]						Section 4.1 and 6.2.2
AZD2811 administration							Section 4.1 and 6.2.1
G-CSF							Section 4.1 and 6.2.4

AE = Adverse event; CBCs = complete blood counts; CRP = C-reactive protein; CSP = Clinical study protocol; CT = Computed tomography; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony stimulating factor; INR = international normalized ratio; IP = Investigational product; IV = Intravenous; MRI = Magnetic resonance imaging; NA = not applicable; PT = prothrombin time; PTT = partial prothrombin time; CCI [redacted]; RC1 = re-treatment cycle 1; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = Serious adverse event; T_3 = Triiodothyronine; T_4 = Thyroxine; TSH = Thyroid-stimulating hormone.

[a] Only if short-acting G-CSF (filgrastim) is administered.

2 INTRODUCTION

2.1 Study Rationale

Despite significant progress in the treatment of extensive stage small-cell lung cancer (ES-SCLC) resulting from the addition of programmed cell death-ligand 1 (PD-L1) immunotherapy to platinum-etoposide, there remains an urgent need for more effective therapies that delay disease progression by prolonging the progression-free survival (PFS) and overall survival (OS) in this disease. Preliminary clinical data suggest that AZD2811 may be effective in stabilizing disease in later line SCLC participants. This trial will investigate whether a similar benefit can be demonstrated in first line (1L) ES-SCLC participants by adding AZD2811 to durvalumab maintenance therapy, following [redacted] of durvalumab plus platinum-etoposide induction therapy. Currently, no benefit is expected from adding AZD2811 to the induction therapy.

2.2 Background

Lung cancer is the second most common cancer and the leading cause of cancer death for men and women. It is estimated that 135,720 (72,500 men and 63,220 women) deaths from this disease will occur in 2020 in the United States (Cancer.Net, 2020 https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics).

Small-cell lung cancer accounts for 10 to 15 percent of all lung cancers. Small-cell lung cancer is perhaps the most aggressive form of the disease, distinguishable from non-SCLC by its rapid doubling time, high growth fraction, and early dissemination. It is strongly associated with tobacco smoking and is also associated with an extremely high mutation rate.

Regardless of stage, the current prognosis for patients with SCLC is unsatisfactory despite improvements in diagnosis and therapy made during the past 25 years. Without treatment, SCLC has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2 to 4 months if untreated. About 10% of the total population of SCLC patients remains free of disease during the 2 years from the start of therapy, which is the time period during which most relapses occur. Even these patients, however, are at risk of dying from lung cancer (both small and non-small cell types) (Fry et al, 1996; Johnson et al, 1990; Lassen et al, 1995; Murray et al, 1993). Limited disease was defined as tumor tissue that could be encompassed in a single radiation port, and ES disease was defined as any tumor that extended beyond the boundaries of a single radiation port. At present, limited disease is identified in ~30% of patients, and ES is identified in ~70% of patients.

Four to six cycles of platinum-based chemotherapy, etoposide in combination with either cisplatin or carboplatin, without maintenance therapy has been the standard care for patients with ES-SCLC for the past 25 years (Pignon et al, 1992), and are recommended by major

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

2.2.1 AZD2811

The mammalian Aurora kinases (A, B, and C) are a family of highly conserved serine/threonine kinases that perform key roles in the regulation of separate points of the cell cycle. The Aurora kinases, and Aurora kinase B in particular, represent potential targets for anticancer therapy.

AZD2811, formerly designated AZD1152 hydroxyl-quinazoline pyrazole anilide, is a potent and selective inhibitor of Aurora B kinase activity and has been incorporated into a nanoparticle (NP) carrier for intravenous (IV) administration (Song et al, 2016). The phosphate pro-drug of AZD2811, known as AZD1152 (barasertib), reached Phase II of clinical development as a continuous IV infusion. The pro-drug was converted rapidly in plasma to the active drug, AZD2811. While promising efficacy was seen with barasertib in the acute myeloid leukemia (AML) population, continuous prolonged IV infusion was required. In addition, barasertib was limited in the solid tumor populations by a high frequency of bone marrow toxicities and little to no clinical response.

AZD2811 has been incorporated into a NP carrier that has been shown to provide prolonged exposure to AZD2811.

Nonclinical studies have shown increased efficacy and decreased toxicity for AZD2811, formulated as a NP, when compared to barasertib treatment in in vivo SCLC and diffuse large B-cell lymphoma models (Ashton et al, 2015; Ashton et al, 2016).

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD2811 is provided in the Investigator's Brochure (IB).

2.2.2 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death-ligand 2 [PD-L2]) with programmed cell death-protein 1 (PD-1) on T cells and cluster of differentiation (Larkin et al)80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of cancer. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that

durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ) (Stewart et al, 2015).

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab therapy are summarized in Section 8.3.12. Refer to the current durvalumab IB for a complete summary of nonclinical and clinical information, including safety, efficacy, and pharmacokinetics (PK).

In March 2020, the United States Food and Drug Administration (FDA) approved the use of durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with ES-SCLC. Efficacy of this combination in patients with previously untreated ES-SCLC was investigated in CASPIAN (NCT03043872), a randomized, multicenter, active-controlled, open-label trial. The CASPIAN trial assessed the benefit of combining durvalumab (± tremelimumab) with etoposide plus either cisplatin or carboplatin (platinum-etoposide standard of care [SOC]) in treatment-naïve patients with ES-SCLC (Paz-Ares et al, 2019). Participants were enrolled between 27 March 2017 and 29 May 2018, for a total of 268 participants allocated to the durvalumab-SOC group and 269 to the SOC group. Durvalumab-SOC was associated with a significant improvement in OS, (hazard ratio: 0.73 [95% confidence interval (CI) 0.59 to 0.91; p = 0.0047]). The median OS was 13.0 months (95% CI 11.5 to 14.8) in the durvalumab-SOC group versus 10.3 months (9.3 to 11.2) in the SOC group. Thirty-four percent (26.9% to 41.0%) versus 25% (18.4% to 31.6%) of patients were alive at 18 months. The study treatment was well tolerated overall, with any-cause adverse events (AEs) (Grade 3 or 4) in 163 (62%) of 265 treated patients in the durvalumab plus SOC group and 166 (62%) of 266 in the SOC group. Adverse events leading to death occurred in 13 (5%) and 15 (6%) patients. Overall, the first-line durvalumab plus SOC significantly improved OS in patients with ES-SCLC versus a clinically relevant control group. Safety findings were consistent with the known safety profiles of all drugs received.

2.2.3 Rationale for Combination of AZD2811 and durvalumab in 1L ES-SCLC

Recent development in segmentation of small cell lung cancer (SCLC) disease into subtypes (Rudin et al, 2019) has, for the first time, enabled rational combination proposals for agents that preferentially target different subtypes (Gay et al, 2021).These subtypes include SCLC-ASCL1 (SCLC-A), -NEUROD1 (SCLC-N) and -POU2F3 (SCLC-P) defined by their eponymous driver transcription factor programs, and a fourth subtype alternatively called SCLC-YAP1 or ‘inflamed’ (SCLC-I), defined by pathobiological features, such as high expression of mesenchymal and inflammatory genes (Rudin et al, 2019; Gay et al, 2021). Analysis of subtype outcome under standard of care treatment including the anti-PDL1 antibody atezolizumab in the Impower133 phase 3 study has shown that the median OS and

the magnitude of benefit with the addition of atezolizumab is numerically greater in SCLC-I compared to the other subtypes. A median OS in SCLC-I of more than 18 months was seen in the Etoposide-Platinum (EP) + atezolizumab arm, compared with just over 10 months in the EP + placebo arm. By contrast, the addition of atezolizumab produced little benefit in SCLC-A and SCLC-N (Gay et al, 2021). However, recently published data from relapsed patients and models demonstrates the inherent plasticity within this tumor type and that subclonal subtype variants can repopulate tumors that previously responded to subtype-selective therapy (Stewart et al, 2020). This plasticity and concomitant heterogeneity which can drive rapid adaptation and relapse therefore requires therapeutic strategies that embody principles of parallel mechanistic targeting, rather than synergy within a specific mechanism, so that the final regimen addresses the therapeutic needs of most patients, and prevents emergent resistance through subtype switching.

CCI [redacted]

CCI [redacted]. However, the hypothesis that inhibition of Aurora kinase B can drive generation of micronuclei in tumor cells (Harding et al, 2017), CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Table 6 Risk Assessment

Identified and potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study interventions		
AZD2811		
Identified risks associated with AZD2811 include: • neutropenia, • febrile neutropenia, • rash, • sepsis. The following are considered potential risks for AZD2811: • lymphocytopenia and leukocytopenia, • anemia, • thrombocytopenia, • stomatitis/oral mucositis, • diarrhoea, • nausea and vomiting, • alopecia/hair loss.	Potential risks for AZD2811 have been determined from nonclinical studies with AZD2811, previous clinical experience with AZD1152 (barasertib), and clinical experience with other drugs targeting inhibition of Aurora kinases.	Toxicity management of AZD2811 is presented in Section 8.5.1. A dermatology consultation is recommended for participants who present with rash. G-CSF is mandatory for every cycle in which participants receive AZD2811.
Durvalumab		
Identified risks associated with durvalumab include: • pneumonitis, • interstitial lung disease, • hepatitis, • diarrhea/colitis, • hypothyroidism, • hyperthyroidism, • blood TSH increased, • blood TSH decreased, • adrenal insufficiency, • type 1 diabetes mellitus, • hypophysitis/hypopituitarism and diabetes insipidus, • nephritis, • rash/dermatitis, • myocarditis,	This section includes identified risks and potential risks for durvalumab of an inflammatory and/or immune-mediated nature, related to the mechanism of action of durvalumab and related to mAb therapeutics in general.	The risks presented can be mitigated through close monitoring, early detection, and prompt treatment with corticosteroids, immunosuppressants, and/or endocrine therapy. Investigators should adhere to the Toxicity Management Guidelines (Section 8.5.2) by performing a thorough evaluation to rule out alternative etiologies.

Table 6 Risk Assessment

Identified and potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
• myositis/polymyositis, • infusion-related reactions, • pancreatitis, • encephalitis. Potential risks for durvalumab include: • other rare or less frequent events with a potential immune-mediated etiology, e.g., pericarditis, sarcoidosis, uveitis, and other events involving the eye (e.g., keratitis and optic neuritis), skin (e.g., scleroderma, vitiligo, and pemphigoid), and hematological (e.g., hemolytic anemia and immune thrombocytopenic purpura), rheumatological events (polymyalgia rheumatic and autoimmune arthritis), neuropathy/neuromuscular toxicities (e.g., myasthenia gravis, Guillain-Barre syndrome), vasculitis, and non-infectious meningitis. • hypersensitivity reactions, including: ° anaphylaxis and allergic reaction ° cytokine release syndrome ° immune complex disease • infections (excluding urinary tract infection, bronchitis, sepsis, bacterial sepsis, and urosepsis)		
Standard of Care		
NA	**Cisplatin:** Cumulative renal toxicity associated with Cisplatin injection is severe. Other major dose-related toxicities are myelosuppression, nausea, and vomiting and other toxicities (vascular, serum electrolyte disturbance, hyperuricemia, neurotoxicity, ocular, and hepatotoxicity). Anaphylactic-like reactions to cisplatin injection have been reported.	Toxicity management of cisplatin, carboplatin, and etoposide will be according to the local labels.

Table 6 Risk Assessment

Identified and potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	Carboplatin: Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Nausea/vomiting is frequently observed as well as urea elevations and electrolyte disturbance. Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. **Etoposide:** Dose-limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. Other possible adverse events are the occurrence of an anaphylactic reaction (chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension), nausea/vomiting, asthenia/malaise, alopecia, chills, and/or fever.	
Study procedures		
	Routine blood draws and disease assessments have a well-established risk profile, which is addressed by the institutional standards. Biopsy-taking is not devoid of risk but is considered unavoidable for determining the type of the disease to be treated.	Biopsy procedures are set up in such a way that the risk for bleeding and other risks are reduced at maximum.
The most serious adverse reactions that may occur during G-CSF treatment include anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, and severe splenomegaly/splenic rupture.	**G-CSF**: The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, chest pain, and neck pain), anemia, vomiting, and nausea. In clinical trials in cancer patients, musculoskeletal pain was mild or moderate in 10% of patients and severe in 3% of patients.	Toxicity management of G-CSF will be according to the local label.
Other		

Table 6 Risk Assessment

Identified and potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	No drugs comparable to AZD2811 are known.	NA

AE = adverse event; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; G-CSF = granulocyte colony stimulating factor; GGT = gamma-glutamyltransferase; IV = intravenous; mAb = monoclonal antibody; NA = not applicable; TSH = thyroid-stimulating hormone.

2.3.2 Benefit Assessment

AZD2811 has demonstrated preliminary activity in relapsing SCLC in an expansion cohort of the AZD2811 first in human trial (NCT02579226). Twenty-one patients who had failed SOC and up to 3 lines of therapy were treated with CCI AZD2811 every CCI Clinical benefit (defined as complete response [CR], partial response [PR], or stable disease [SD] ≥ 8 weeks) was demonstrated in > 50% of the participants, and median OS in this patient population was 9.95 months (data on record).

The monotherapy safety profile of durvalumab and AZD2811 suggest that both drugs can be combined in the absence of overlapping toxicities. Both drugs have demonstrated clinical benefit in SCLC and there is clear medical need to improve the efficacy of the current therapy in ES-SCLC. Therefore, investigating the efficacy of the combination of durvalumab with AZD2811 is a rational next step.

2.3.3 Overall Benefit: Risk Conclusion

The risks related to the current chemotherapy SOC (platinum-etoposide) for ES-SCLC are well known and widely documented to be myelosuppression and nausea/vomiting. The benefits are well recognized, resulting in this treatment being universally used to treat 1L SCLC patients for many years. The risks are well understood, and an extensive concomitant therapy guideline and practice has been put in place that follows Institutional Guidelines considered most appropriate to work in the lowest risk setting as much as feasible. Extensive stage-SCLC, with the exception of adding PD-L1 immunotherapy such as durvalumab to the current Platinum-Etoposide standard, has had no real therapeutic improvement for many years. A wide range of new and less new therapies have been explored, but all with dismal effect (Amarasena et al, 2015; Fiegl et al, 2014; Kalemkerian and Schneider, 2017).

AZD2811 has demonstrated preliminary clinical benefit, stabilizing disease, in an extension Phase I cohort of patients with relapsing SCLC that had been treated with between 1 to 3 prior lines of therapy. It is therefore anticipated that AZD2811 is highly likely to have a similar disease-stabilizing effect when used in the earlier 1L maintenance setting. The potential risks

associated with patients being exposed to AZD2811 are considered to be outweighed by the benefit, as observed in the late line setting.

The benefit of durvalumab in combination with platinum-etoposide for the treatment of ES-SCLC was demonstrated in the CASPIAN trial, which resulted in regulatory approval in Singapore in February 2020 and by the FDA in March 2020. Durvalumab has also been recommended for approval in the European Union (EU) by the Committee for Medicinal Products for Human Use for ES-SCLC.

More detailed information about the known and expected benefits and potential risks of AZD2811 and durvalumab may be found in the IBs for AZD2811 and durvalumab.

Taking into account the extensive monitoring and safety measures proposed in this study to minimize risk to participants, and the potential risks identified for durvalumab and AZD2811 as maintenance therapy, the anticipated benefits that may be afforded to participants with ES-SCLC are justified.

3 OBJECTIVES AND ENDPOINTS

Table 7 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of AZD2811 + durvalumab by assessment of the proportion of participants alive and progression free at 12 months APF12 who have not progressed during EP-durvalumab based induction therapy.	The proportion of participants alive and progression free at 12 months APF12 will be defined as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by the investigator at local site at 12 months, in participants who enter the maintenance phase.
Secondary	
To evaluate efficacy of AZD2811 + durvalumab by assessment of the proportion of participants alive at 12 months OS12, 15 months OS15, and 18 months OS18 who have not progressed during EP-durvalumab based induction therapy.	The proportion of participants alive at 12 months OS12, 15 months OS15, and 18 months OS18 will be defined as the Kaplan-Meier estimate of OS at 12 months, 15 months, and 18 months, respectively, in participants who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of the proportion of participants alive and progression free at 6 months APF6 and 9 months APF9 who have not progressed during EP-durvalumab based induction therapy.	The proportion of participants alive and progression free at 6 months APF6 and 9 months APF9 will be defined as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by the investigator at local site at 6 months and 9 months, respectively, in participants who enter the maintenance phase.
To evaluate efficacy of EP-durvalumab by assessment of Objective response rate (ORR in the induction phase.	ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed CR or PR, by the investigator at local site per RECIST v1.1 in the induction phase (all participants).
To evaluate efficacy of AZD2811 + durvalumab by assessment of ORR in the participants who had not progressed during EP-durvalumab based induction therapy.	ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed CR or PR, by the investigator at local site per RECIST v1.1, in participants who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of PFS in participants who had not progressed during EP-durvalumab based induction therapy.	PFS is defined as time from date of first dose study intervention in the induction phase until progression per RECIST v1.1 or death due to any cause. The median Kaplan-Meier estimate in participants who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of OS in participants who had not progressed during EP-durvalumab based induction therapy.	OS is defined as time from date of first dose study intervention in the induction phase until the date of death due to any cause. The median Kaplan-Meier estimate in participants who enter the maintenance phase.
To assess the safety and tolerability profile of study intervention in SCLC.	Safety and tolerability will be evaluated in terms of AEs, vital signs, physical examination, clinical chemistry, TSH, PT/PTT/INR, hematology, ECG, and urinalysis, as well as

Table 7 Objectives and Endpoints

Objectives	Endpoints
	treatment delays, dose reductions, and dose discontinuations.
To evaluate the PK of durvalumab and AZD2811.	Concentration of durvalumab, and AZD2811 and its metabolite in serum and whole blood, respectively.
To evaluate the effect of AZD2811 + durvalumab on SCLC symptoms and health-related QoL using EORTC QLQ-C30 and QLQ-LC13.	EORTC QLQ-C30: Symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Health-related QoL/functioning (physical function, role function, emotional function, cognitive function, social function, and global health status/QoL). EORTC QLQ-LC13: Disease-related symptoms (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and other pain).
CCI [redacted]	

Table 7 Objectives and Endpoints

CCI

[redacted]

Table 7 Objectives and Endpoints

AE = adverse event; APF6 = proportion of participants alive and progression free at 6 months from first dose of study therapy in the induction phase (ie, PFS rate at 6 months); APF9 = proportion of participants alive at 9 months from the first dose of study therapy in the induction phase (ie, PFS rate at 9 months); APF12 = proportion of participants alive and progression free at 12 months from first dose of study therapy in the induction phase (ie, PFS rate at 12 months); CR = complete response; [redacted]; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EP = etoposide and platinum-based chemotherapy; [redacted] INR = international normalized ratio; KM = Kaplan-Meier; ORR = objective response rate; OS = overall survival; OS12 = proportion of participants alive at 12 months (ie, OS rate at 12 months); OS15 = proportion of participants alive at 15 months (ie, OS rate at 15 months); OS18 = proportion of participants alive at 18 months (ie, OS rate at 18 months); PD = progressive disease; [redacted] PFS = progression-free survival; PFS2 = progression-free survival after subsequent anticancer therapy; PK = pharmacokinetics; PR = partial response; PT = prothrombin time; PTT = partial prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumors; [redacted]; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-LC13 = 13-item Lung Cancer Quality of Life Questionnaire; QoL = quality of life; SCLC = small-cell lung cancer; [redacted]; TSH = thyroid-stimulating hormone.

4 STUDY DESIGN

4.1 Overall Design

On 14 December 2021 AstraZeneca took the decision to terminate enrolment for this study prior to completion due to the evolving benefit risk profile of AZD2811 that does not support further development for the first-line treatment of patients with extensive stage small-cell lung cancer. Patients already enrolled in the study were able to continue. However, no further patients were permitted to start AZD2811 treatment and ongoing patients transitioning into the maintenance phase after this date were offered durvalumab monotherapy. As a result of the early termination, the data cut-off for the final analysis in this study is planned for 18 June 2022.

Sections from CSP v8.0 are retained throughout this protocol for reference. Clinical Study Protocol v8.0 was prepared to include urgent safety measures via a Dear Investigator Letter; however, CSP V 8.0 was not implemented due to early termination. Clinical Study Protocol v8.0 is superseded by CSP v9.0.

This is a Phase II, open-label, multicenter, single arm, global study to determine the efficacy, safety, and tolerability of AZD2811 + durvalumab maintenance therapy in patients with ES-SCLC who do not progress during etoposide and platinum-based chemotherapy (EP) combined with durvalumab induction therapy as first-line treatment. A schematic diagram of the study is presented in Figure 1.

This study plans to assign treatment to approximately 100 eligible participants at sites worldwide and treatment will be conducted in 2 phases – an initial induction phase followed by a maintenance phase.

Tumor assessments are scheduled at screening as baseline with follow-up assessments every 6 weeks (Q6W; ± 1 week) up to Week 36 following the date of first administration of induction therapy and every 8 weeks (Q8W) ± 1 week thereafter until confirmed objective disease progression, unless the investigator, in agreement with the Sponsor, agrees otherwise. For patients eligible to receive AZD2811 treatment, every effort should be made to schedule the scan within 1 week prior to dosing with AZD2811; scan results **MUST** be reviewed prior to dosing to confirm the absence of disease progression.

Global recruitment will be complete when approximately 100 participants have been assigned in the induction phase and a minimum of 80 evaluable participants have entered the maintenance phase. It is anticipated that assigning treatment to approximately 100 eligible participants into the induction phase will achieve the minimum of 80 evaluable participants required for the maintenance phase. In the event that 100 participants does not yield the minimum of 80 evaluable participants in the maintenance phase, additional participants will

be enrolled and assigned into the study. In the event that a biomarker is identified that is associated with improved efficacy, additional participants may be recruited. Study participants who fail screening can be rescreened a single time.

4.1.1 Induction Phase

Participants who fulfil all the inclusion criteria and none of the exclusion criteria will be treated for CCI on a CCI schedule in the induction phase with platinum-based induction therapy (cisplatin or carboplatin plus etoposide) + durvalumab according to Table 8 and Section 6.1.

Table 8 Study Intervention During the Induction Phase

Order of Administration	Agent and Dose	Route	Duration	Observation Time	Schedule
1	Durvalumab (CCI	IV	CCI		
2	Carboplatin (AUC 5-6)	IV			
	OR Cisplatin (75-80 mg/m^2)	IV			
3	Etoposide (80-100 mg/m^2)	IV			

Note: Participants whose weight falls to 30 kg or below (≤ 30 kg) should receive weight-based dosing equivalent to 20 mg/kg of durvalumab CCI until the weight improves to > 30 kg, at which point the participant should start receiving the fixed dosing of durvalumab CCI. The doses of cisplatin and carboplatin should be calculated on C of each treatment cycle.
AUC = area under the curve; CCI EP = etoposide and platinum-based chemotherapy; IV = Intravenous; PIG = per Institutional Guidelines; CCI.

At the end of this induction phase, participants will be assessed for disease progression, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Participants who AstraZeneca and the investigator determine may not continue treatment after progressive disease during the induction phase will be followed up for AE/serious adverse event (SAE) reporting for 90 days following the final dose of study intervention.

Following confirmed disease progression, further therapy will be offered by the investigator.

4.1.2 Maintenance Phase

4.1.2.1 Maintenance Phase Overview

Participants who have not progressed per RECIST v1.1 at the end of the induction phase and who meet maintenance phase eligibility criteria will continue into the maintenance phase of the trial and be treated with AZD2811 + durvalumab as maintenance therapy (Table 9) until radiological progressive disease (PD), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (Section 7.1).

Table 9 Study Intervention During the Maintenance Phase

Day and order of administration in each cycle	Agent and dose	Route	Duration	Observation time	Schedule
CCI	AZD2811 CCI [a]	IV	CCI		
	Durvalumab CCI	IV			
	Filgrastim 0.5 MU (5 µg)/kg/day SC from CCI (DAILY until at least CCI of each cycle AND the ANC has recovered to ≥ 1.5×10^9/L) or Neulasta (pegfilgrastim) 6 mg dose SC on CCI only	SC			

[a] Dose reduction levels are provided in Section 6.6.1

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

ANC = absolute neutrophil count; G-CSF = granulocyte colony stimulating factor; IV = intravenous; MU = million units; N/A = not applicable; PD = progressive disease; CCI; SC = subcutaneously.

Hematopoietic growth factors (short-acting granulocyte colony stimulating factor [G-CSF] [filgrastim] or long-acting G-CSF [pegfilgrastim]), must be administered as primary prophylaxis on/from CCI of every maintenance cycle to limit the duration of neutropenia, and to minimize the risk of neutropenic fever and infections. If short-acting G-CSF (filgrastim) is used, administer DAILY until at least CCI of each cycle AND the ANC has recovered to $\geq 1.5 \times 10^9$/L. Long-acting G-CSF should be administered once only per cycle on CCI

For all participants who are treated through progression with durvalumab monotherapy, the investigator should ensure participants do not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment would not further benefit the participant. AZD2811 must not be administered through progression.

4.1.2.2 Safety Run-In

CCI

Nevertheless, because the amount of safety data on this combination is still expected to be from a limited number (≤ 6) of participants when this trial starts, a safety run-in will be conducted, in which six participants will be followed for (at least) 1 cycle to assess safety of the AZD2811 + durvalumab combination. The study procedures and safety assessments undertaken for the safety run-in period will be as per the Schedule of Activities (Table 1). The safety run-in will comprise participants as defined in the inclusion and exclusion criteria (Section 5.1 and 5.2) to provide the earliest opportunity to assess tolerability of the combination in those six participants.

After administration of the first dose of AZD2811 + durvalumab to the first participant, at least 24 hours must be allowed before administration to the second participant in case of unexpected acute toxicity.

A participant will be evaluable for the safety run-in (described as dose-limiting toxicity [DLT]) safety assessment if they have received at least 75% of the scheduled AZD2811 and durvalumab doses, or had a DLT. Non-evaluable participants will be replaced. After the completion of ≥ CCI (≥ 1 cycle) dosing in the first 6 evaluable maintenance therapy

participants, all available safety data (including, but not limited to, DLTs, adverse events of special interest (AESIs), laboratory safety assessments, and clinical examinations) will be assessed to judge if the combination is safe and tolerable. This assessment, and subsequent decision to continue dosing further participants, will be undertaken by the SRC. The SRC membership is described in Appendix A 5. The role and responsibilities of SRC members, as well as the purpose and timing of the SRC meetings, are described in the SRC Charter.

The purpose of the safety run-in is to confirm the dose of AZD2811 and durvalumab in the combination setting. Treatment of new participants entering the maintenance phase with AZD2811 + durvalumab will be paused (after ~six participants) while the SRC convenes to assess the safety data at the end of the safety run-in phase if a DLT event is observed in any of the first ~six participants. In absence of clarity on the feasibility of the proposed combination maintenance therapy, transition of participants beyond the approximately six participants to the maintenance therapy, can be paused until confirmation of feasibility. In the event of a pause, new participants entering the maintenance phase would receive treatment with durvalumab monotherapy, as this represents standard of care treatment for ES-SCLC patients. Following a pause, if dosing with AZD2811 resumes, participants receiving durvalumab monotherapy will be allowed to start dosing with AZD2811 if maintenance phase eligibility criteria are met. In the absence of a DLT event in any of the first ~six participants, treatment with AZD2811 + durvalumab into the maintenance phase will not be paused while the SRC convenes. Participants from the safety run-in phase will contribute to the required treatment assignment as described in Section 9.3.

4.1.2.2.1 Results of the Safety Run-In

Treatment in the maintenance phase of the trial began in June 2021 and the SRC completed an initial assessment of the safety run-in cohort in September 2021. While no DLTs were experienced by the first six participants, one participant experienced an SAE of neutropenic sepsis with a fatal outcome and one participant experienced an SAE of febrile neutropenia with a fatal outcome during the second cycle of AZD2811 treatment (ie, CCI Both SAEs were attributed to AZD2811 treatment by the investigators. Additional information about these events and the identified risk of sepsis has been added to the Investigator's Brochure.

Treatment with AZD2811, of new participants entering the maintenance phase, was put on hold while additional data analyses were conducted, and the following protocol amendments were proposed to ensure the safety of current and future participants:

- Maximum AZD2811 dose permitted will be CCI ; maintenance phase eligibility criteria must be confirmed prior to dosing the first cycle of AZD2811
- AZD2811 must not be administered if there is any suspicion of disease progression. Every effort should be made to schedule tumour evaluation scans within 1 week prior

to dosing with AZD2811; scan results **MUST** be reviewed prior to dosing to confirm the absence of disease progression.

- AZD2811 must not be administered if there is any suspicion of infection; consider (prophylactic) antibiotics for participants experiencing Grade 4 ANC or at a high risk of infection. If infection is suspected, work up should be performed to identify whether there is an infection.

- AZD2811 dose will be reduced if a patient experiences Grade 4 ANC, irrespective of time to recovery

- An additional safety visit on Day 12 of [redacted]) has been introduced to identify low ANC earlier in the cycle (from Phase I experience, the nadir is expected between 10 to 15 days after AZD2811 dosing).

After implementation of the above recommendations in CSP v8.0, an additional safety run-in cohort will be assessed by the SRC according to Section 4.1.2.2.

4.1.3 DLT Criteria

A DLT will be considered for any toxicity observed unless unequivocally due to underlying malignancy or an extraneous cause.

The DLT evaluation period is defined as the first [redacted] from the start of AZD2811 + durvalumab administration. Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. The definition of an evaluable participant is found in Section 4.1.4. The following toxicities constitute a DLT:

- Grade 4 neutropenia, or febrile neutropenia.
- Grade 4 anemia.
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding.
- Concurrent Grade ≥ 3 total bilirubin (TBL), hepatic transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) and alkaline phosphatase lasting > 48 hours, or any change in liver function test results consistent with Hy's Law (HL; see Appendix E).
- Any ≥ Grade 3 non-hematologic AE with the exception of:
  - Grade 3 nausea, vomiting, stomatitis, and/or diarrhea that is controlled within 4 days with standard supportive care. Use of prophylactic mouthwash to prevent stomatitis is allowed and should be used according to local site practices.
  - Grade 3 fatigue and/or decreased appetite (anorexia) that resolves within 5 days

  - Grade 3 elevations in ALT/AST that return to initial eligibility criteria within 7 days of study drug interruption.
- Inability to receive ≥ 75% of all doses in Cycle 1 of maintenance due to treatment--related toxicity.
- Non-hematologic toxicity of ≥ Grade 3 (at any time during treatment) that, in the judgment of the investigators and the Study Physician, is dose limiting.

4.1.4 Definition of DLT-Evaluable Participants

An evaluable participant for the purpose of the safety run-in decision is defined as a participant who has received AZD2811 + durvalumab and either:

- Has completed the minimum safety evaluation requirements of the study (ie, safety assessments in the SoA [Table 1] up to and including CCI in Cycle 1 maintenance of AZD2811 + durvalumab) and received at least 75% of the scheduled AZD2811 and durvalumab doses, or
- Has experienced a DLT in Cycle 1 of maintenance therapy

4.1.5 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 (e.g., during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with 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 participant'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 study participants, maintain compliance with Good Clinical Practice (GCP), and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (e.g., hospital policies) or local government, these changes may include the following options:

- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated Study Physician.

- Home or 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 participants 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 H.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for [redacted] of Induction Therapy

The use of platinum-based chemotherapy in combination with etoposide has been SOC for SCLC for over 40 years. Current investigations are now adding immunotherapeutics to chemotherapeutics to broaden antitumor responses. In March 2020, the FDA approved the use of durvalumab in combination with 4 cycles of etoposide and either carboplatin or cisplatin, and durvalumab in maintenance therapy, as first-line treatment of patients with ES-SCLC. Efficacy of this combination in patients with previously untreated ES-SCLC was investigated in CASPIAN, a randomized, multicenter, active-controlled, open-label trial. The evaluation was based on the comparison of patients randomized to durvalumab plus chemotherapy, followed by durvalumab maintenance therapy, versus chemotherapy alone. Median OS was 13.0 months in the durvalumab plus chemotherapy arm and shown to be superior compared to 10.3 months in the chemotherapy alone arm having 6 cycles of chemotherapy (Paz-Ares et al, 2019). As such, 4 cycles of chemotherapy, when combined with durvalumab and followed by durvalumab maintenance therapy, appears to be superior to 6 cycles of chemotherapy alone.

The durvalumab + platinum-based induction chemotherapy induction regimen will be administered for [redacted] followed, in participants who do not have PD at the end of induction, by AZD2811 + durvalumab combination maintenance therapy [redacted] until disease progression or unacceptable toxicity.

4.2.2 Rationale for AZD2811 and Durvalumab Maintenance Therapy

The interest of durvalumab in 1L ES-SCLC has been established with giving durvalumab in combination with platinum-etoposide and in maintenance therapy in terms of landmark 12-month PFS and OS, as demonstrated in the CASPIAN study. AZD2811 has demonstrated activity in relapsing SCLC in an expansion cohort of the AZD2811 first in human trial (NCT02579226). Twenty-one patients who had failed SOC and up to 3 lines of therapy were treated with [redacted] AZD2811 [redacted] Clinical benefit (defined as CR, PR, or SD $\geq$ 8 weeks) was demonstrated in > 50% of the participants, and median OS in this patient population was 9.95 months (data on record).

Nonclinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1) can have a positive effect on disease control in SCLC patients, as described in Section 2.2.2.

The therapy safety profile of durvalumab and AZD2811 suggest that both drugs can be combined in the absence of overlapping toxicities. Both drugs have demonstrated clinical benefit in SCLC, and there is clear medical need to improve the efficacy of the current therapy in ES-SCLC. Therefore, investigating the efficacy of the combination of durvalumab with AZD2811 is a rational next step.

4.3 Justification for Dose

4.3.1 Rationale for Dose of Platinum-based Chemotherapy

The doses of platinum-based chemotherapy to be used in this study are the approved doses for this indication.

4.3.2 Rationale for Dose of AZD2811

The initial proposed AZD2811 dosing schedule, CCI on CCI with mandatory G-CSF on CCI is based on data from a Phase I dose escalation and expansion study: D6130C00001/NCT02579226.

In Part A of study D6130C00001, several AZD2811 dosing schedules were evaluated. Doses ranging from CCI AZD2811 were administered IV on CCI of every C CI cycle. After switching to single day treatment per cycle, the cycle length was shortened to cycles of CCI duration to decrease time between infusions and increase the dose intensity, evaluating doses ranging from CCI to CCI mg infused on Day 1. On CCI G-CSF was introduced and mandated to ensure recovery of neutrophils before Day 1 of the next cycle. AZD2811 CCI on CCI with mandatory G-CSF on CCI was declared the maximum tolerated dose (MTD) and recommended Phase II dose. Activity and safety of this regimen was further supported by data from a dose expansion phase: D6130C00001 Part B.

Exposure-response analysis of data from D6130C00001 indicates that an AZD2811 dose above CCI would result in unfavorable rates of severe (Grade 4) neutropenia, further supporting the proposed AZD2811 dosing schedule. Therefore, G-CSF is mandated for this dose and schedule. Further details of the results from Study D6130C00001 are available in the AZD2811 IB.

Subsequent to the review of the safety run-in cohort of the current study (see Section 4.1.2.2.1), the starting dose of AZD2811, in combination with durvalumab in the maintenance phase, has been reduced to a maximum of CCI on CCI with mandatory G-CSF on/from CCI to decrease the rate of Grade 4 neutropenia.

Dose reductions for AZD2811 are detailed in Section 6.6.1.

4.3.3 Rationale for Dose of Durvalumab

The dosing schedule proposed during the induction phase is aligned with the standard fixed dosing of CCI durvalumab for CCI of CCI duration followed by durvalumab maintenance therapy, which is supported by efficacy and safety as well as tolerability data from the CASPIAN clinical trial.

The durvalumab dosing regimen during the maintenance phase was aligned to the AZD2811 CCI regimen with standard fixed dosing of CCI durvalumab CCI The proposed durvalumab regimen is dose-matched (ie, equivalent dose per week) to the regimen tested in the CASPIAN clinical trial maintenance setting – durvalumab CCI every CCI dosing – and further supported by preliminary safety as well as tolerability data from the HUDSON (NCT03334617) clinical trial.

4.4 End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last treated participant in the study, globally.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP or if the site is unable to recruit sufficient numbers of participants into the study.

The AstraZeneca Study Team may also terminate the study prematurely if concerns for safety arise within this study or in any other study with any agent used in this study.

As a result of the early termination of this study, the data cut-off (DCO) for the final analysis is planned for 18 June 2022, approximately 5 months after last participant first dose.Main data collection will stop at that point.Data analysis will be performed and a clinical report will be written based on this dataset. Serious AEs will be collected per Section 8.3.2.

Participants who are receiving treatment at the time of DCO can either choose to discontinue from the study or, when the investigator believes participants are gaining clinical benefit, may continue to receive study treatment, following discussion with, and approval from, the AstraZeneca Study Team.

Patients' treatment may be continued:

- Within the current study, or
- Within a rollover or safety extension study, if available, or

- Within a drug supply program (commercial supply or other compassionate use program), if applicable

In case of treatment continuation within the current study:

- Assessments will revert to standard of care at each site
- There will be no further data collection, except SAE reporting. The Clinical Study Database will be closed
- Paper form process will be used for SAE reporting. All SAEs, overdoses and pregnancies would be reported until 30 days after last dose
- Investigational product will be supplied to sites manually outside of the IXRS system. Drug dispensation and reconciliation will be handled by site at each patient's visit
- Study will remain open until last patient completes treatment. Last Subject Last Visit will be defined as the last patient's treatment discontinuation

In case a rollover or safety extension study is available for patients remaining in this study after analysis is finalized, they may be transferred to one of these studies:

- A rollover or safety extension study would have to be fully approved by Regulatory and Ethics bodies applicable for the patient's site
- The new study would ensure proper treatment continuation with visit assessments per its own protocol
- Visit assessments would cover the minimum needed for safety oversight. May also cover assessments required for long term use analysis
- Any patient that was to move to such a study would need to be reconsented beforehand

If study drug is approved in a given market for use in the disease under study, patients may be discontinued and switched to marketed product. Drug supply options will vary depending on the specific country and would be proposed to patients if they are considered the best way to continue treatment by both AZ and the investigator.

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

5 STUDY POPULATION

Extensive stage-SCLC treatment naïve patients who have not progressed per RECIST v1.1 after induction with EP-durvalumab comprise the study population. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Induction Phase Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥ 18 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Histologically or cytologically documented extensive stage (American Joint Committee on Cancer Stage [7th edition] IV SCLC [T any, N any, M1 a/b]), or T3 or T4 tumor stage due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

- Brain metastases; must be asymptomatic or treated and stable off steroids and anti-convulsants for at least one month prior to study treatment. Participants with suspected brain metastases at screening should have a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain prior to study entry.

3 Provision of an archived tumor tissue block or unstained slides if block cannot be provisioned) where such samples exist. If not, a mandatory fresh biopsy will be required at screening (refer to Section 8.6.2.1 and Laboratory Manual for details).

4 Participants must be considered suitable to receive a platinum-based chemotherapy regimen, combined with durvalumab, as first-line treatment for the ES-SCLC. Chemotherapy must contain either cisplatin or carboplatin in combination with etoposide.

5 Life expectancy ≥ 12 weeks.

6 World Health Organization (WHO) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 at treatment assignment.

7 Body weight > 30 kg.

8 At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥ 15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST v1.1 guidelines.

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

10 Adequate organ and marrow function as defined below:

- Hemoglobin ≥ 9.0 g/dL (without blood transfusion in the last 2 weeks).
- 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 (without platelet transfusion in the last 2 weeks).
- Serum bilirubin ≤ 1.5 × the upper limit of normal (ULN). This will not apply to participants with known Gilbert's syndrome, who will be allowed to participate in the study, in consultation with their physicians.
- In participants without hepatic metastasis: ALT and AST ≤ 2.5 × ULN.
- In participants with hepatic metastases, ALT and AST ≤ 5 × ULN.
- Measured or calculated creatinine clearance (CL): > 60 mL/min for participants on cisplatin and > 50 mL/min for participants on carboplatin, as determined by Cockcroft-Gault (using actual body weight):
- Males:

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

- Females:

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

Informed Consent

11 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

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

5.2 Induction Phase Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Medical contraindication to etoposide-platinum (carboplatin or cisplatin) based chemotherapy and/or durvalumab, including a history of immune mediated reactions, e.g. pneumonitis.

2 Any history of radiotherapy to the chest prior to systemic therapy or planned consolidation chest radiation therapy. Radiation therapy outside of the chest for palliative care or prophylaxis (e.g. bone metastasis or prophylactic cranial irradiation (PCI) for

brain metastases) is allowed, but must be completed before first dose of the study medication.

3 i) Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer related conditions (e.g., hormone replacement therapy) is acceptable.

ii) For the first six patients that are in the safety run-in group only: Concomitant use of the clinical BCRP inhibitors curcumin, cyclosporine A or eltrombopag. Culinary use of spices containing curcumin, such as curry and turmeric, is acceptable.

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

5 History of allogeneic organ transplantation.

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

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

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

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

9 History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of IP and of low potential risk for recurrence

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of malignant disease

10 History of leptomeningeal carcinomatosis.

11 History of active primary immunodeficiency.

12 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, or human immunodeficiency virus (HIV; positive HIV 1/2 antibodies). Participants with a past or resolved HBV infection, or vaccination (defined as the presence of hepatitis B core antibody and absence of HbsAg), are eligible. Participants positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (Nguyen et al). Participants suspected for COVID-19 infection will need to have a negative screen test before treatment assignment. If a COVID-19 test is performed, the results should be reported in the EDC.

Prior/Concomitant Therapy

13 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 (e.g., 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 (e.g., CT scan premedication). Premedication with steroids for chemotherapy is acceptable.

14 Receipt of live, attenuated vaccine within 90 days prior to the first dose of study intervention. Note: Participants, if assigned, should not receive live vaccine while receiving study intervention and up to 90 days after the last dose of study intervention.

15 Known allergy or hypersensitivity to AZD2811, durvalumab, etoposide, carboplatin, cisplatin, or any of their excipients (e.g., polyethylene glycol [PEG]).

16 Participant has had prescription or non-prescription drugs, or other products known to be strong inhibitors/inducers of CYP3A4 that cannot be discontinued prior to Day 1 of the maintenance phase (refer to Section 6.5.1 for list of drugs and specific washout periods) and withheld throughout the maintenance phase until 2 weeks after the last dose of study drug.

17 Prior randomization or treatment in a previous AZD2811 or durvalumab clinical study regardless of treatment arm assignment.

Prior/Concurrent Clinical Study Experience

18 Previous treatment assignment in the present study, except for participants meeting criteria for re-treatment after relapse.

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

20 Participation in another clinical study with a study intervention during the last 4 weeks prior to Cycle 1 Day 1.

Other Exclusions

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

22 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

23 Female participants who are pregnant or breastfeeding, or male or female participants of reproductive potential who are not willing to employ effective birth control from screening to 7 months after the last dose durvalumab + EP or AZD2811 + durvalumab (Section 5.3).

5.3 Maintenance Phase Eligbility Criteria

In order to continue study treatment in the maintenance phase of the study (ie, CCI and beyond), participants must meet the following criteria prior to initiating dosing with AZD2811.

5.3.1 Maintenance Phase Inclusion Criteria

1 Body weight > 30 kg.

2 Adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1.5×10^9/L.
- Platelet count ≥ 75×10^9/L.
- Serum bilirubin ≤ 1.5 × ULN.
- In participants without hepatic metastasis: ALT and AST ≤ 2.5 × ULN.
- In participants with hepatic metastases: ALT and AST ≤ 5 × ULN.
- Measured or calculated creatinine CL: > 50 mL/min, as determined by Cockcroft-Gault (using actual body weight) (see Section 5.1).

5.3.2 Maintenance Phase Exclusion Criteria

1 Progressive disease as per RECIST v1.1 guidelines. A scan must have been performed within 1 week prior to first dose of AZD2811.

5.4 Lifestyle Considerations

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

- Female participants of childbearing potential who are sexually active with a non-sterilized male partner must use at least 2 highly effective methods of contraception (see Table 10) from the time of screening and must agree to continue using such precautions for 7 months after the last dose of AZD2811 and/or durvalumab, whichever is the longer time period. Male partners of a female participant must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Female participants should refrain from breastfeeding throughout this period. In addition, female participants must refrain from egg donation while on study and for 7 months after the final dose of AZD2811 and/or durvalumab, whichever is the longer time period.
- Non-sterilized male participants who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 9 months after the last dose of study drug. Male participants should refrain from sperm donation for 9 months after the last dose of AZD2811 and/or durvalumab, whichever is the longer time period. Female partners of a male participant must use a highly effective method of contraception throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as 12 months with no menses without an alternative medical cause).

Acceptable non-hormonal birth control methods include:

- Total/True abstinence: When the participant refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study and for at least 7 months after the last dose of study drug. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a study) and withdrawal are not acceptable methods of contraception.
- Vasectomized sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.

- Tubal occlusion PLUS male condom.
- Intrauterine device PLUS male condom. Coils must be copper-banded.

Highly effective methods of contraception are described in Table 10. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (e.g., 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 10 Highly effective methods of contraception (< 1% failure rate)

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

[a] This is also considered a hormonal method.

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants 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 SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only one rescreening is allowed in the study. Participants must complete the

rescreening within 4 weeks of the initial screenfail date (maximum of 7 weeks between initial consent and Cycle 1 Day 1 or second screen failure). Rescreened participants should be assigned the same participant number as for the initial screening.

Individuals who start induction therapy and are later found not to be eligible, should be discussed with the Study Physician before the next treatment.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol. Study interventions are described in Table 11 and details of dosing levels and order of dosing for the induction and maintenance phases are provided in Table 8 and Table 9, respectively. For dose modifications of AZD2811, please see Section 6.6.1. For information on rescue medication(s), please refer to Section 6.5.4

Table 11 Study Interventions

Phase of treatment	Study intervention	Duration of study intervention
Induction Phase	Durvalumab + Carboplatin or Cisplatin + Etoposide	CCI, unless objective disease progression is observed during induction phase
Maintenance Phase	AZD2811 + Durvalumab + G-CSF	Until objective disease progression [a]

[a] Participants are treated until progressive disease in the maintenance phase unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.
G-CSF = granulocyte colony stimulating factor.

Participants must receive platinum-based chemotherapy and durvalumab for the first CCI. Participants without evidence of PD (per RECIST v1.1) who meet maintenance phase eligibility criteria will receive AZD2811 and durvalumab and G-CSF during the maintenance phase.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

AstraZeneca will supply AZD2811 and durvalumab. Refer to Table 12 for information on investigational study interventions.

Dose reductions for toxicity are only permitted for AZD2811; the dose of durvalumab can be delayed for toxicities, but dose reductions are not allowed (see Section 6.6). Participants must be eligible to receive both durvalumab and AZD2811 to enter the maintenance phase.

Table 12 List of Investigational Study Interventions

Intervention name	AZD2811	Durvalumab
Dose form	CCI	
Dosage level(s)	Induction phase: N/A Maintenance phase: CCI	Induction phase: CCI Maintenance phase: CCI
Route of administration	IV infusion	IV infusion
Handling instructions	Refer to Handling Instructions manual	Refer to Handling Instructions manual
Dosing instructions	See Table 9 and Section 6.2.1 plus Section 6.6.1 for dose reductions	See Table 8 (Induction Phase), Table 9 (Maintenance Phase) and Section 6.2.2
Packaging and labeling	Study intervention will be provided in CCI vials. Each CCI vial will be labeled as required per country requirement	Study intervention will be provided in CCI vials. Each CCI vial will be labeled as required per country requirement
Provider	AstraZeneca	AstraZeneca

IV = intravenous; N/A = not applicable; CCI.

6.1.2 Non-investigational Products

The chemotherapy agents (etoposide, cisplatin, and carboplatin) and G-CSF will either be locally sourced or, under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, which will be labeled in the local language in accordance with regulatory guidelines (Table 13). In the EU, etoposide, cisplatin, carboplatin, and G-CSF are considered auxiliary medicinal products according to EU clinical trials guidance (EU, 2017).

Chemotherapy is considered a "non-investigational drug" as it is a recommended SOC in international guidelines. Chemotherapy will be administered in accordance with the recommendation in international guidelines (NCCN, 2020).

Platinum-based chemotherapy should continue for CCI. Chemotherapy dosing will be as described in Table 13.

Each chemotherapy agent will be administered in accordance with local guidelines and premedication will be provided.

If any chemotherapy agent is permanently discontinued early (prior to completing CCI) as a result of a toxicity, e.g. hypersensitivity reaction, may enter the maintenance phase after consultation with the Study Physician, and as long as the participant meets the maintenance

phase eligibility criteria. However, if any chemotherapy agent is permanently discontinued early (prior to completing CCI) as a result of disease progression during induction, the participant will not enter the maintenance phase.

Hematopoietic growth factors (short-acting G-CSF [filgrastim] or long-acting G-CSF [pegfilgrastim], see Section 6.2.4), must be administered as primary prophylaxis on/from CCI of every maintenance phase cycle to limit the duration of neutropenia, and to minimize the risk of neutropenic fever and infections caused by AZD2811 (Table 13). If short-acting G-CSF (filgrastim) is administered, DAILY dosing should continue until at least CCI AND the measured neutrophil nadir is passed (expected between Days CCI after AZD2811 dosing) and the neutrophil count has recovered to $\geq 1.5 \times 10^9$/L. Long-acting G-CSF should be administered once only per cycle on CCI

Table 13 Non-Investigational Medicinal Products for this Study

Intervention name	Etoposide	Cisplatin OR carboplatin	G-CSF
Dose form	Liquid for infusion	Liquid for infusion	Liquid for infusion
Dosage level(s)	Etoposide 80–100 mg/m² CCI	Investigator's choice of carboplatin AUC 5–6 mg/mL/min or cisplatin 75–80 mg/m² CCI	Filgrastim 0.5 MU (5 µg)/kg/day SC from CCI (DAILY until at least CCI of each cycle AND the ANC has recovered to $\geq 1.5 \times 10^9$/L) or Neulasta (pegfilgrastim) 6 mg dose SC on CCI
Route of administration	IV infusion	IV infusion	SC
Use	Background treatment	Background treatment	Supportive therapy
Sourcing	Provided locally by the study site[a]	Provided locally by the study site[a]	Provided locally by the study site[a]

[a] Under certain circumstances when local sourcing is not feasible, a SOC treatment may be supplied centrally through AstraZeneca.

ANC = absolute neutrophil count; AUC = area under the curve; G-CSF = granulocyte colony stimulating factor; IV = intravenous; MU = million units; PIG = per Institutional Guidelines; CCI ; SC = subcutaneous; SOC = standard of care.

6.1.3 Duration of Treatment and Criteria for Treatment After Initial Assessment of PD

Maintenance treatment will start on CCI . Participants who do not have any evidence of radiological disease progression during the induction phase (CCI of EP-durvalumab)

and who meet maintenance phase eligibility criteria (see Section 5.3) will continue into the maintenance phase of the trial.

In the rare instances when the RECIST v1.1-defined radiological findings are considered equivocal by the investigator or there is doubt whether or not there is evidence of objective progression (e.g., technical issues, including image artifacts), the participant may not move into the maintenance phase of the study without prior discussion with the Sponsor.

Upon initial assessment of PD, treatment with AZD2811 must be discontinued. Treatment with durvalumab may be continued until radiological PD is confirmed by the subsequent scan, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Participants with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system [CNS] metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue study treatment. All efforts should be put in place to perform a disease assessment to document this disease progression.

Post final data cut-off

Participants who are receiving treatment at the time of DCO can either choose to discontinue from the study or, when the investigator believes participants are gaining clinical benefit, may continue to receive study treatment, following discussion with, and approval from, the AstraZeneca Study Team. For participants continuing to receive study treatment following the final DCO and database closure assessments will revert to standard of care.

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled and assigned study treatment may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Handling Instruction.

6.2.1 AZD2811

AZD2811 is presented as a [CCI], contained in a [CCI] glass vial, containing approximately [CCI] of suspension at an AZD2811 concentration of [CCI]. The cartons and vials will be individually labeled.

AZD2811 IP vials must be stored [CCI]; for specific storage conditions, please see the product label.

Preparation of AZD2811 doses for administration

Refer to the AZD2811 Handling Instructions manual (provided separately to study centers) for information on the product vial thawing procedure and dose preparation.

AZD2811 must **not** be infused through an administration set containing a 0.2-µm or 0.22-µm filter, whereas durvalumab must be infused through a 0.2-µm or 0.22-µm filter. Therefore, AZD2811 and durvalumab must be infused through **different** infusion lines.

6.2.2 Durvalumab

Durvalumab will be supplied by AstraZeneca as a [CCI] vial concentrate for solution for infusion. It has a label-claim volume of [CCI] and a density of [CCI]

Investigational product vials are stored refrigerated in original packaging until use to prevent prolonged light exposure. For specific storage conditions, please see the product label.

Preparation of durvalumab doses for administration with an IV bag

Refer to the Durvalumab Handling Instructions manual (provided separately to study centers) for information on dose preparation.

Durvalumab must be infused through a 0.2-µm or 0.22-µm filter, whereas AZD2811 must **not** be infused through a 0.2-µm or 0.22-µm filter. Therefore, the products must be infused through **different** infusion lines.

6.2.3 Standard of Care: EP

Etoposide and platinum-based chemotherapy will be locally sourced or centrally supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, and it will be labeled with local language translated text in accordance with regulatory guidelines.

6.2.4 G-CSF

Granulocyte-CSF (filgrastim or pegfilgrastim including generic formulations of each) will be locally sourced and will be administered according to prescribing information or treatment guidance in general use by the Investigating site.

Granulocyte-CSF (filgrastim or pegfilgrastim including generic formulations of each) must be administered on CCI as a primary prophylaxis. Granulocyte-CSF (filgrastim) daily dosing should continue until at least CCI and the measured neutrophil nadir is passed (expected between CCI after AZD2811 dosing) and the neutrophil count has recovered to $\geq 1.5 \times 10^9$/L, and must be discontinued 48 hours prior to the next dose of AZD2811. Note: PEGylated G-CSF, e.g., pegfilgrastim, may not be given later than CCI (in a CCI cycle) due to its long half-life. Complete blood counts should be collected and reviewed on Days 8, 12 (Cycles 5 and 6) and/or 15 at a minimum, or more frequently as clinically indicated.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label, non-randomized study. All participants will receive the study intervention. Participants will receive a participant number when the informed consent is signed. A cap of 25% of participants receiving cisplatin will be applied and managed through the interactive voice/web response system (IXRS). A cap of 10% of participants with brain or CNS metastases will be applied and managed using the IXRS. Data will be reviewed on a regular basis by the medical study team in order to ensure the safety of the participants.

6.4 Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and start and stop times of treatments administered in the clinic will be recorded in the source documents and in the electronic Case Report Form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff, other than the person administering the study intervention.

6.5 Concomitant Therapy

All medications, including vaccines, over-the-counter medications, prescription medications, vitamins, and/or herbal supplements from the time of ICF until end of study treatment will be recorded in the source and eCRF. The name of the therapy, reason for use, start/stop dates of administration, dose, and frequency will be recorded, in addition to:

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

- Was this “Break-through pain-therapy Yes/No”, where break-through pain-therapy is defined as therapy taken for pain at the choice of the participant in addition to the usual daily dose

Participants will be asked to complete a simple diary to record breakthrough pain medication use, and the data will be entered into the EDC.

Antibiotics taken within 90 days of Cycle 1 Day 1 will be recorded in the CRF.

The Study Physician should be contacted if there are any questions regarding concomitant therapy.

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

6.5.1 Permitted Concomitant Medication

6.5.1.1 Permitted Concomitant Medication for AZD2811

Permitted concomitant medication for AZD2811 include the following:

- No routine prophylactic antiemetics or premedication will be given during maintenance therapy. However, these medications may be administered for symptoms when they occur and may be given prophylactically afterwards.
- Supportive care and other medications that are considered necessary for the participant’s wellbeing may be given at the discretion of the investigator and should be reported accordingly. AZD2811 must not be administered if there is any suspicion of infection; consider (prophylactic) antibiotics for participants experiencing Grade 4 ANC or at a high risk of infection. If infection is suspected, work up should be performed to identify whether there is an infection.
- Participants already receiving erythropoietin at the time of screening may continue to receive it, provided they have been receiving it for more than one month at the time study intervention is started. Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and thereafter.
- Participants may receive treatment with megestrol acetate when prescribed for appetite stimulation.
- Participants may take low dose warfarin or a coumarin preparation for port prophylaxis.

6.5.1.2 Permitted Concomitant Medication for Durvalumab

Permitted supportive concomitant medications for durvalumab are provided in Table 14. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.5.2).

Table 14 Supportive medications for durvalumab

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed below in Section 6.5.2.2	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all participants
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.5.2 Prohibited Concomitant Medication and Treatments

6.5.2.1 Prohibited Concomitant Medication for AZD2811

To ensure participant safety, the following potent inhibitors of CYP3A4 must not be used during the maintenance phase for any participant receiving AZD2811. While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions. A complete list, which is updated regularly, may be found here https://drug-interactions.medicine.iu.edu/MainTable.aspx:

- ketoconazole,
- itraconazole,
- ritonavir,
- indinavir,
- saquinavir,
- telithromycin,
- clarithromycin, and
- nelfinavir.

For participants taking any of the above, the required washout period prior to the maintenance phase is one week.

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers should be avoided:

- phenytoin,
- rifampicin,
- rifapentine,
- rifabutin,
- carbamazepine,
- phenobarbitone,
- nevirapine,
- modafinil, and
- St John's Wort (Hypericum perforatum).

For participants taking any of the above, the required washout periods prior to starting the maintenance phase are 5 weeks for phenobarbitone, and 3 weeks for any of the others.

Herbal supplements that strongly modulate CYP3A4 must not be used during the maintenance phase. The use of other (or combinations of) natural/herbal products that may modulate CYP3A4 should be discouraged.

After entry into the maintenance phase, if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the participant's safety and welfare, the investigator must contact the Study Physician. A decision to allow the participant to continue in the study will be made on a case-by-case basis.

During the maintenance phase, metformin should be used with caution. AZD2811 has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin.

Preclinical data suggests that AZD2811 is a substrate for BCRP. To allow for accurate assessment of the safety of the combination of AZD2811 and durvalumab, clinical inhibitors of BCRP (curcumin, cyclosporine A, eltrombopag) are not permitted in the first six patients in the trial that form part of the safety run-in group.

6.5.2.2 Prohibited Concomitant Medication and Treatments for Durvalumab

Prohibited concomitant medication and treatments for durvalumab are presented in Table 15.

Table 15 Prohibited concomitant medications for durvalumab

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the participant is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the participant is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the participant is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Live attenuated vaccines	Should not be given from 90 days before through 90 days after the last dose of study intervention
Immunosuppressive medications, including but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the IP infusions. The following are allowed exceptions: Use of immunosuppressive medications for the management of IP-related AEs, Use in participants with contrast allergies. In addition, use of inhaled, topical, and intranasal corticosteroids are permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management or prevention of nonimmunotherapy related events experienced by the participant (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc)
EGFR TKIs	Should not be given concomitantly Should be used with caution in the 90 days post last dose of durvalumab Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first generation EGFR TKIs) has been reported when durvalumab has been given concomitantly

Table 15 Prohibited concomitant medications for durvalumab

Prohibited medication/class of drug:	Usage:
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

AE = adverse event; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; EGFR = epidermal growth factor receptor; IP = investigational product; mAb = monoclonal antibody; PD-1 = programmed cell death-protein 1; PD-L1 = programmed death-ligand 1; TKI = tyrosine kinase inhibitor.

6.5.3 Drug-drug Interactions

6.5.3.1 AZD2811 Drug-drug Interactions

AZD2811 is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, AZD2811 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the metabolism of AZD2811 is CYP3A4.

6.5.3.2 Durvalumab Drug-drug Interactions

There is no information to date on drug-drug interactions with durvalumab either non-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 mechanism of action of durvalumab involves binding to PD-L1, and therefore significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring will be conducted to evaluate any potential drug-drug interactions.

6.5.4 Rescue Medicine

As a result of immune-mediated AEs (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 (e.g., for colitis) and mycophenolate (e.g., for hepatitis). Generic/biosimilar versions of rescue drugs are allowable if approved in the treating country. 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 dispensed by the unblinded pharmacist (if supplied centrally) and stored according to the labelled storage conditions, with

temperature excursions reported accordingly by the unblinded pharmacist. If required for use as a result of an imAE, then the IXRS will provide to the pharmacists the kit identification number to be allocated to the participant at the time.

6.6 Dose Modification

6.6.1 Dose Modification for AZD2811

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of AZD2811, as appropriate. Dose reductions and/or holds and initiations of supportive care are allowed as clinically indicated by the treating physician (Section 8.5.2).

The starting dose of AZD2811 is CCI to be given every CCI with GCSF on/from CCI . Dosing and dose adjustments are shown in Table 16.

Table 16 Dose Modification for AZD2811

Dose level	Agent and Dose	Route	Duration	Observation Time	Schedule
Dose level 1	AZD2811 CCI	IV	CCI	CCI	
Dose level -1	AZD2811 CCI	IV		CCI	
Dose level -2	AZD2811 CCI	IV		CCI	

IV = intravenous; CCI .

6.6.2 Dose Modification for Durvalumab

Dose delays are permitted (see Dosing Modification and Toxicity Management Guidelines referenced in Section 8.5.2). **However, dose reduction of durvalumab is not permitted.** If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered. Dosing may be delayed due to either an immune or a non-immune-related AE. If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible. The durvalumab dose may be delayed for up to a maximum of 12 weeks from initiation of corticosteroids; see Section 8.5.2 for additional details.

6.6.3 Dose Modification of Platinum-based Chemotherapy, Cisplatin, and/or Carboplatin

Dose modification of EP-based chemotherapy, cisplatin, and/or carboplatin will be according to the package insert and local SOC.

6.7 Intervention After the End of the Study

Participants, having reached the end of study, should be followed according to Section 1.3. See also Section 7.1.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

If either durvalumab or AZD2811 administration is to be permanently discontinued, administration of the other study intervention may continue as monotherapy if the investigator considers that the participant will gain benefit. If participants are receiving durvalumab monotherapy, the schedule of activities may be reduced to Day 1 visits and assessments only. Scans must be performed at the frequency stated in the SoA.

It may be necessary for a participant to permanently discontinue all study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety assessment (until resolution or absence of improvement), as well as for disease progression and/or death, whichever occurs first. See the SoA (Table 4) for data to be collected at the time of discontinuation of study intervention and follow-up, and for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study or end of study.

An individual participant will not receive any further study intervention if any of the following occur in the participant in question:

- Withdrawal of consent from further treatment with study intervention. The participant is, at any time, free to discontinue treatment, without prejudice to further treatment. Withdrawal from study intervention treatment does not mean withdrawal from study, and the participant is normally expected to continue to participate in the study (e.g., for safety and survival follow-up). If they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3), then they will be withdrawn from the study.
- 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 8.5).
- 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 study intervention (e.g., refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including, or not, another investigational agent.
- Clinical progression and investigator determination that the participant is no longer benefiting from treatment with study intervention.
- Confirmed radiological progression (refer to Appendix F).

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up, and for any further evaluations that need to be completed.

7.1.1 Re-treatment Following Relapse

A participant who has been treated for a minimum of 2 years and continues to experience CR, PR, or SD, as demonstrated by radiographic measures, may be considered for treatment discontinuation. Data from other immunotherapy studies suggest that patients who initially derive clinical benefit from immunotherapy can derive benefit again once the subject has PD while off therapy (Hamid et al, 2013; Wolchok et al, 2013).

Participants who progress during the first 52 weeks after the last dose of study treatment will be eligible for retreatment with the combination of AZD2811 and durvalumab (same dose and schedule as at the time of discontinuation) after consultation with, and in agreement with, the Sponsor. The investigator may consider SOC chemotherapy backbone with the experimental

agent(s) as appropriate for the participants at the time of retreatment. The exclusion criteria listed below **must not** apply:

1 Meets any of the study intervention discontinuation criteria (Section 7.1);
2 ECOG performance status (PS) > 2;
3 Rapid PD or threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention;
4 Participant has had severe/refractory imAE or development of new autoimmune condition that, in the opinion of the investigator, poses undue risk to the participant.
5 Participant has received any other anticancer treatment for their disease following initial study intervention discontinuation

This option for retreatment will be limited to one occasion, and will apply only if the study protocol is still active, ie, the final database lock has not yet occurred. The participant will need to follow the SoA as described in Section 1.3. Participants must also be reconsented.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her/their own request, or may be withdrawn at any time at the discretion of the investigator for reasons including, but not limited to, safety, behavioral, and/or compliance. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records). Documentation of the scope of withdrawal and follow-up permissions must be clearly documented in the source. The Global Study Team should be informed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected up to the date of withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. Where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled into the study, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites, or of the study as a whole, are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

A Web-Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in this study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness, and timelines of the data recorded and the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed unless in the event of a civil crisis, natural disaster, or public health crisis (see Section 4.1.5 and Appendix H).
- Immediate safety concerns should be discussed with the Sponsor immediately upon awareness to determine if the participant should continue or discontinue study intervention, or if other actions are required.

- Adherence to the study design requirements, including those specified in the SoA, are required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be approximately 100 mL at screening and will not exceed approximately 430 mL during any 8 week period whilst on study treatment. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

Given the decision on 14 December 2021 to terminate enrolment, the abbreviated CSR will focus on reporting of safety endpoints. Therefore, the efficacy analyses will be streamlined (see Section 9.4.2 for further detail) and this will be fully documented in the SAP. Sections from CSP v8.0 are retained below for reference.

This study will evaluate the primary endpoint of proportion of participants alive and progression free at 12 months (APF12) from first dose of study therapy in the induction phase, who have moved to the maintenance phase. Secondary efficacy assessments are of proportion of participants alive at 12, 15, and 18 months from first dose of study therapy in the induction phase (OS12, OS15, and OS18), proportion of participants alive and progression free at 6 months and 9 months from first dose of study therapy in the induction phase (APF6, APF9), OS from the first dose of study therapy in the induction phase, PFS from first dose of study therapy in the induction phase, and objective response rate (ORR) from first dose of study therapy. The PFS and ORR endpoints will be derived (by AstraZeneca) from site investigator assessment, according to RECIST v1.1. The primary and secondary endpoints will be assessed for participants who enter the maintenance phase. The ORR will also be assessed for all participants in the induction phase and for the participants who enter the maintenance phase.

From CSP v8.0, the starting dose of AZD2811 in the maintenance phase will be [redacted], the study will therefore primarily report efficacy for the [redacted] dose. Due to early termination of enrolment, CSPv8 was never implemented and no new patients started treatment with

AZD2811; all new patients transitioning into the maintenance phase were treated with durvalumab monotherapy. Further sensitivity analyses will be defined in the SAP.

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

The RECIST v1.1 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 Cycle 1 Day 1 while another one will need to be ensured in the third week of CCI of the induction therapy. Only participants with a RECIST response of CR, PR, or SD will enter the maintenance phase (CR or PR does not need to be confirmed). The RECIST v1.1 assessments of baseline images identify target (defined measurable) and non-target lesions (NTLs), and each lesion (and any new lesion) is evaluated in subsequent, on-treatment follow-up images. This allows determination of follow-up target lesion (Hassel et al) response, NTL response, and overall time point tumor responses (CR, PR, SD, PD, or not evaluable [NE]). The methods of assessment used at baseline should be used at each subsequent follow-up assessment.

From the investigator's review of the imaging scans, the RECIST tumor response data will be used to determine each participant's visit response according to RECIST v1.1. At each visit, participants will be programmatically assigned a RECIST v1.1 visit response of CR, PR, SD, or PD, using information from TLs, NTLs, and new lesions, and depending on the status of their disease compared with baseline and previous assessments. If a participant has had a tumor assessment that cannot be evaluated, then the participant will be assigned a visit response of NE unless there is evidence of progression, in which case the response will be assigned as PD. Please refer to Appendix F for additional detail on RECIST.

Efficacy will be assessed on images collected CCI ± 1 week for the first 36 weeks relative to the date of first dose of study intervention in the induction period, and CCI ± 1 week thereafter until confirmed objective disease progression or the participant is off-study. It is important to follow the assessment schedule as closely as possible (refer to the SoAs in Table 1, Table 3 , and Table 4). Where possible, every effort should be made to schedule the scan within 1 week prior to dosing with AZD2811; scan results **MUST** be reviewed prior to dosing to confirm the absence of disease progression. If disease progression is suspected, an unscheduled imaging assessment should be performed. If an unscheduled imaging assessment is performed and the participant has not progressed, every attempt should be made to perform the subsequent assessments at his or her next regularly scheduled imaging visit.

AstraZeneca requests that at least one subsequent scan is acquired after each initial progression event for all participants, across all arms of the study, no earlier than 4 weeks after and no later than the next regularly scheduled imaging visit after the initial progression event.

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

Following objective disease progression, participants should continue to be followed up for survival every 2 months (8 weeks) as outlined in the follow-up SoA (Table 4); this may be done via telephone contact. In addition, all participants will be contacted in the week following DCO to confirm survival status.

8.1.1 Reading of Scans

Although scan assessments will be performed by investigators, all images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization for quality control and storage in the event that central review is required. Management of participants will be based solely upon the results of the RECIST v1.1 assessment conducted by the investigator.

8.1.2 Survival Assessments

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

8.2 Safety Assessments

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

For participants starting the maintenance phase with durvalumab monotherapy, who subsequently receive AZD2811 in a later cycle (ie, beyond CCI additional safety assessments and PK sampling are required. For example, if a participant receives their first dose of AZD2811 in CCI all safety and PK assessments must be performed as if for Cycle 5. Additional safety assessments must be performed for the first C cycles of AZD2811 treatment, and PK sampling must be completed for the first C cycles of AZD2811 treatment (following the SoA for Cycles CCI

8.2.1 Physical Examinations

- A full physical examination will be performed and include assessments of the following: General appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities), and routinely performed neurological exam.
- A targeted physical examination will be based on symptoms and will include, at a minimum, assessments of the regions considered abnormal at study entry and those indicated by clinical observation. Special attention should be paid to participants with skin abnormalities in their medical history and/or observed at baseline, as well as abnormalities appearing during trial treatment. Any skin changes should be assessed and documented throughout the study.

Physical examination will be performed at time points as specified in the SoA and will need special attention for skin alteration if observed at study entry. Situations in which physical examination results should be reported as AEs are described in Section 8.3.5.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA.

Vital signs (blood pressure (systolic/diastolic), pulse rate, body temperature, and respiration rate) will be evaluated according to the assessment schedules (Section 1.3). Body weight is also recorded at each visit, along with vital signs.

Height should be collected at screening only.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5. For any AEs of infusion reactions, please enter the vital signs values into the case report form.

8.2.3 Electrocardiograms

An electrocardiogram (ECG) will be performed at time points as specified in the SoA. Electrocardiograms should be obtained after the participant has been in a supine position for 5 minutes and recorded while the participant remains in that position. Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study (see Section 1.3). All participants will have triplicate 12-lead ECGs (about 5 minutes apart). The ECG needs to be performed prior to the onset of the IV therapy (AZD2811 + durvalumab) and approximately 15 minutes after the end of all IV therapies.

During Induction, if there are clinically relevant cardiac observations during an infusion, triplicate 12-lead ECGs (about 5 minutes apart), pre- and post-durvalumab infusion

(approximately 15 minutes of the end of infusion) should be performed at all subsequent infusions.

During Maintenance, if there are clinically relevant cardiac observations during an infusion, triplicate 12-lead ECGs (about 5 minutes apart) pre- and post-AZD2811 and pre- and post-durvalumab infusion (approximately 15 minutes of the end of infusion) should be performed at all subsequent infusions.

In case of clinically significant ECG abnormalities, including a Fridericia's Correction Formula (QTcF) value > 470 ms, 2 additional 12-lead ECGs should be obtained over a brief period, at 15 and 30 minutes, to confirm the finding. Sites may also report Bazett's Correction Formula (QTcB) if that is the local standard.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, and other safety tests will be taken at the times indicated in the assessment schedules and as clinically indicated (see Section 1.3).

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

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

The laboratory variables to be measured are presented in Table 17 (clinical chemistry), Table 18 (hematology), Table 19 (urinalysis), and Table 20 (other safety tests).

Other safety tests to be performed at screening include assessment for HbsAg, hepatitis C antibodies, and HIV antibodies. Tuberculosis test will be performed as per Institutional Guidelines at screening.

Table 17 Clinical Chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[d]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH
Chloride[c]	T_3 free(reflex)
Creatinine clearance	T_4 free(reflex)
C-reactive protein[e]	Urea or blood urea nitrogen, depending on local practice
Creatinine	Carbon Dioxide[c]
Gamma glutamyl transferase	
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥ 2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only one of these parameters is routinely measured, either lipase or amylase is acceptable.
[c] Bicarbonate should be performed where standard. Carbon dioxide may be performed in place of bicarbonate, where standard.
[d] Magnesium required at screening and Cycle 1 Day 1, and then should be performed only as clinically indicated or per local practice.
[e] Not required at all time points; refer to the Schedule of Activities tables in Section 1.3
AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; T_3 = Triiodothyronine; T_4 = Thyroxine; TSH = Thyroid-stimulating hormone.

Table 18 Hematology

Full White Blood Cell Count Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils[a]	Red Blood Cells
	Hematocrit
Hemoglobin	Platelet count
HbA1c (baseline only)	Total white cell count
Reticulocytes [a]	

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

Table 19 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

Table 20 Other Safety Tests
Coagulation Tests: prothrombin time, partial prothrombin time, international normalized ratio, fibrinogen.
HbsAg, hepatitis C antibodies, and HIV antibodies
Tuberculosis test is required at screening; method of testing will be according to Institutional Guidelines
Pregnancy test: Women of Childbearing Potential Only; serum is required at screening and within 3 days of Cycle 1 Day 1; urine may be used at future visits. Pregnancy testing will be performed monthly (28 +/- 7 days) through 90 days post last dose or until a new treatment is initiated, whichever is shorter.

If a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of HL. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria. All participants meeting the criteria for HL should have further chemistry profiles performed at 28 days (± 3 days), 2 months (± 1 week), and 3 months (± 1 week) after permanent discontinuation of IP (see Appendix E).

After completion of Cycle 1, a new cycle of treatment may begin when the absolute neutrophil count (ANC) is ≥ 1.5×10^9/L and the platelet count is ≥ 75×10^9/L, and any other clinically relevant adverse effects have resolved or reverted to baseline. The next cycle may be delayed up to 14 days until ANC is ≥ 1.5×10^9/L, and the platelet count is ≥ 75 x 10^9/L or returned to baseline (see Section 8.5.1).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and the date, time of collection, and results (values, units, and reference ranges) should be recorded on the appropriate eCRF.

Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All participants with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory

values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.5 Early Participant Review for Safety

Participants will be evaluated 15 days after the first dose of each cycle of chemotherapy and on Days 8 and 15 of each maintenance cycle to ensure early identification and management of toxicities by the investigator. Participants will also be evaluated on Day 12 of Cycles [redacted] (the first [redacted] cycles of AZD2811 treatment).

8.2.6 WHO ECOG Performance Status

World Health Organization ECOG PS will be assessed at the times specified in the assessment schedules (see Section 1.3), based on the following:

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

1 Restricted in strenuous activity but ambulatory and able to carry out light work or work of a sedentary nature (e.g., 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.

8.2.7 Other Safety Assessments

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

Pneumonitis (ILD) Investigation

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

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc.), including auscultation for lung field, will be assessed
- SpO_2
  - Saturation of peripheral oxygen (SpO_2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured, where possible:
    - ILD markers (KL-6, SP-D) and β-D-glucan
    - Tumor markers: Particular tumor markers, which are related to disease progression
    - Additional Clinical chemistry: CRP, lactate dehydrogenase

8.3 Adverse Events and Serious Adverse Events

The PI 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.

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

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events, including SAEs, will be collected from time of signing the ICF throughout the treatment period and including the follow-up period (90 days after the last dose of study intervention) as specified in the SoA (see Section 1.3).

If the investigator becomes aware of an SAE with a suspected causal relationship to the IP that occurs after the end of the clinical study in a participant, the investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

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

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date, and time where relevant, when the AE started and stopped
- Initial and maximal CTCAE grade
- Assessment of seriousness
- Assessment of relatedness to the study intervention - AZD2811 and durvalumab
- Action taken with regard to IP(s) as well as the use of supportive treatment
- AE caused participant's withdrawal from study (yes or no)
- Outcome

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

- Date investigator became aware of SAE
- Where applicable, dates of hospitalization and discharge
- In the event of death, date of death, probable cause of death, autopsy performed with details
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between IP 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 should also be assessed for other medication and study procedures. Note: 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.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider, 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 eCRF. 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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR). Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs, ECGs, and clinical/neurological assessment(s) should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or are considered to be clinically relevant as judged by the investigator (which may include, but not be limited to, consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or drug interruption).

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 (e.g., 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 (DUS).

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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.

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the DUS 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.

8.3.8 Disease Under Study

Symptoms of DUS are those which might be expected to occur as a direct result of SCLC. Events that are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.3.9 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, investigators or other site personnel will 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 will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one 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 will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

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

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness is the IB for AZD2811, the IB for durvalumab, and the local labels for etoposide, carboplatin, cisplatin, and G-CSF.

8.3.10 Pregnancy

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

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

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

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **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 provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

When the eCRF module is used, include the following: The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 9 months after the last dose of AZD2811 and/or durvalumab, whichever is the longer time period. Please follow the local prescribing information relating to contraception.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) occurring from the date of the first dose until 90 days after the last dose of study intervention should, if possible, be followed up and documented.

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

Participants who are permanently discontinued from further receipt of study intervention, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see the SoAs [Table 4]).

8.3.11 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 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.3.12 Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to an understanding of the study intervention and may require close monitoring. An AESI may be serious or nonserious. 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 study intervention.

8.3.12.1 AESIs for AZD2811

There are no AESIs currently identified for AZD2811.

8.3.12.2 AESIs for Durvalumab

Adverse events of special interest 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 mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the investigator has any questions with regard 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 (e.g., presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.5.2). 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.

8.4 Overdose

For guidance, refer to AstraZeneca standard operating procedure: Reporting of Individual Safety Events in Clinical Studies.

For this study, any dose of study intervention greater than the doses shown in Table 12 and Table 11 (or reduced, as indicated in Table 21 and Table 22), given CCI will be considered an overdose.

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Management of Study Intervention-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 study intervention along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and the approach taken.
- During the maintenance phase, if a participant needs to discontinue one of the study interventions, they may continue on study taking only the other study intervention.

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

8.5.1 Specific Toxicity Management and Dose Modification Information – AZD2811

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of AZD2811, as appropriate. Dose reductions and/or holds are allowed as clinically indicated by the treating physician, according to Table 21 and Table 22. AZD2811 dosing should be delayed if there is any suspicion that a participant is suffering from an infection. In addition, there are certain circumstances in which AZD2811 should be permanently discontinued (Section 7.1).

Dose reductions of AZD2811 should be considered if the toxicity is considered to be related to AZD2811. Dose re-escalation for individual participants is permitted on a case-by-case basis following discussion between the Study Physician and the investigator.

In general, if a participant experiences a Grade 1 or Grade 2 non-hematologic toxicity, no dose modification is required (except dose modifications for skin toxicities in Table 22). If a participant experiences a clinically significant and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, dosing will be interrupted, or the dose reduced, and supportive therapy administered as suggested by the treating physician.

If the toxicity resolves or reverts to NCI CTCAE ≤ Grade 1 or baseline within 14 days of onset and the participant is showing clinical benefit, treatment with AZD2811 may be restarted using the rules below for dose modifications (see Table 21) and with discussion and agreement with the Study Physician as needed.

If any toxicity does not resolve to NCI CTCAE ≤ Grade 1 or baseline after 14 days (Day 35 of the cycle), then the participant should be withdrawn from AZD2811 treatment and observed until resolution of the toxicity (see Table 21). Any participant who develops a Grade 3 or 4 non-hematologic toxicity that does not resolve to ≤ Grade 1 or baseline within 14 days should be removed from AZD2811 treatment unless approved by the Study Physician to continue treatment.

In the event of dose delays, the visit cycles will be calibrated such that Day 1 of each cycle is the date that the participant receives the dose.

Table 21 Dose Modification for Non-skin Toxicity

NCI CTCAE v5.0 Toxicity Grade	Action
For all toxicities leading to a dose hold, discontinue AZD2811 treatment if the toxicity does not resolve to NCI CTCAE ≤ Grade 1 or baseline after 14 days (ie, by Day 35 of a cycle), with exceptions noted below.	
Non-Hematologic Toxicity	
Grade 3 non-hematologic toxicity lasts > 4 but ≤ 7 days and resolves to ≤ Grade 1 or baseline	• At first occurrence, consider restarting at the same dose • If second occurrence (≤ 7 days) Grade 3, reduce to dose level -1 • If third time: Reduce to dose level -2 and discuss risk-benefit analysis with Study Physician
Toxicity remains Grade 3 > 7 days (despite supportive therapy)	• At first occurrence, reduce one dose level • If second occurrence, reduce to dose level -2 and discuss risk-benefit analysis with Study Physician
Grade 4 non-hematologic toxicity lasts> 4 but ≤ 7 days and resolves to ≤ Grade 1 or baseline	• At first occurrence, reduce to dose level -1 • If second time: Discuss with Study Physician whether risk-benefit analysis supports continuation
Grade 4 non-hematologic toxicity lasts > 7 days	Discuss with Study Physician whether risk-benefit analysis supports continuation
Grade 3 or 4 non-hematologic toxicity that does not resolve to ≤ Grade 1 or baseline within 14 days	Discontinue study treatment unless approved by the Study Physician to continue
Sepsis, or any other Grade 3 or 4 non-hematological toxicity, not expected to be manageable/reversible with dose reduction	Discontinue study drug
Hematologic Toxicity	
Participants can only be dosed with AZD2811 on Day 1 of any Cycle if the ANC is ≥ 1.5×10^9/L and the platelet count is ≥ 75×10^9/L.	
Grade 0-3 (except as noted below)	Maintain dose
Grade 2-3 ANC; or Grade 2-3 thrombocytopenia without bleeding or requirement for platelet transfusion	• Hold until recovery and then maintain dose
Grade 3 thrombocytopenia with bleeding or requiring a platelet transfusion; or Grade 4 ANC	• First occurrence: Hold until recovery and then reduce to dose level -1 • Second occurrence: Dose reduce to level -2 and discuss with Study Physician whether risk-benefit analysis supports continuation

Table 21 Dose Modification for Non-skin Toxicity

NCI CTCAE v5.0 Toxicity Grade	Action
Febrile neutropenia; or Grade 4 thrombocytopenia	• First occurrence: Hold until recovery and then reduce to dose level -2 • Second occurrence: Discontinue treatment

ANC = absolute neutrophil count; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Skin Toxicity

Special attention should be paid to skin observation in participants having skin alterations in their medical history.

Participants will be monitored for appearance of pruritus and/or any signs of rash, including erythematous rash, exfoliative rash, maculo-papular rash, and skin exfoliation throughout study treatment. Participants experiencing skin toxicity should have the following dose modifications applied (see Table 22).

Table 22 Dose Modification for Skin Toxicity

Toxicity	Occurrence	Action
Grade 1: Painless erythema, mild or localized pruritus, rash/acne intervention not indicated, rash/desquamation macular or papular eruption, or erythema without associated symptoms.	Any occurrence	Institute supportive measures, such as topical therapy for symptomatic relief, and continue therapy.
Grade 2: Painful erythema, intense or widespread pruritus, rash/acne intervention indicated, rash/desquamation macular or papular eruption with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of BSA. Superficial ulceration < 2 cm; local wound care; medical intervention indicated.	Any occurrence	Institute supportive measures, such as topical therapy for symptomatic relief. Dose reduction or dose hold at the investigator's discretion. Participants requiring > 2 dose reductions will discontinue AZD2811.
Grade ≥ 3: Erythema with desquamation, pruritus intense or widespread interfering with ADL, rash/acne associated with pain requiring narcotic analgesics, ulceration or desquamation, rash/desquamation severe generalized erythroderma or macular or popular or vesicular eruption; desquamation covering ≥ 50% of BSA. Superficial ulceration ≥ 2 cm; local wound care; medical intervention indicated.	Any occurrence	Institute supportive measures, such as topical therapy for symptomatic relief, and interrupt AZD2811 until toxicity has resolved to Grade ≤ 1. When resuming treatment after a dose interruption, if obtained within 3 weeks, reduce AZD2811 by one dose level. If toxicity has not returned to Grade ≤ 1 in 3 weeks, treatment cannot be resumed without approval of the Sponsor. Participants requiring > 2 dose reductions will discontinue AZD2811.

ADL = activities of daily living; BSA = body surface area.

8.5.2 Specific Toxicity Management and Dose Modification Information – Durvalumab

In territories where Durvalumab is approved for the treatment of ES-SCLC, toxicity management and dose modification should follow local recommendations (e.g. in the US follow the USPI). In territories where Durvalumab is not approved for the treatment of ES-SCLC, toxicity management and dose modification should follow the Toxicity Management Guidelines (TMGs) described below and provided to the investigative site as an Annex document.

Comprehensive TMGs have been developed to assist investigators with the recognition and management of toxicities associated with the use of durvalumab. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with durvalumab, with specific instructions for dose modifications (including discontinuations) and treatment interventions.

Investigators are advised, however, to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

Participants 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 study intervention, 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.

8.6 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study -specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

- PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Any residual back-up PK samples may be used for future exploratory biomarker research or diagnostic development related to cancer and/or drug action (in this case, residual back-up PK samples will be shipped to an AstraZeneca-assigned biobank – see details in the Laboratory Manual) subject to optional participant consent.

8.6.1 Pharmacokinetics

- Whole blood samples will be collected for measurement of whole blood concentrations of AZD2811 and metabolites, as specified in the SoA.
- Serum samples will be collected for measurement of serum concentrations of durvalumab, as specified in the SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Sponsor, e.g., for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.6.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in whole blood (AZD2811 and metabolite) or serum (durvalumab) will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

In addition, blood or plasma samples may be subjected to further analyses in order to investigate the released and/or encapsulated AZD2811, and other AZD2811 metabolites. These analyses, if any, will be reported outside of the CSR.

8.6.2 CCI

CCI

8.6.2.1 CCI

CCI

CCI

[redacted]

8.6.2.2 CCI

CCI

[redacted]

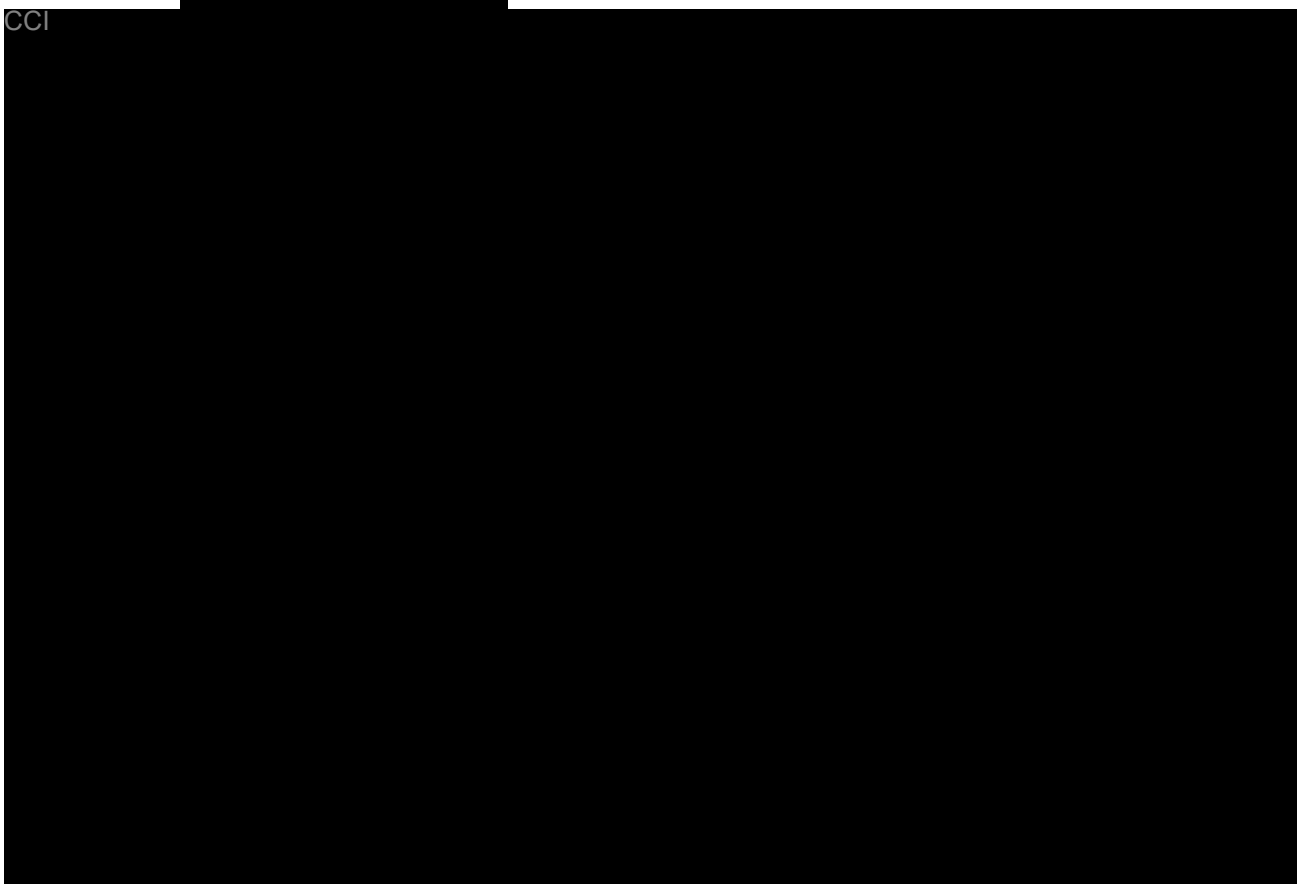
CCI

8.6.2.3 CCI

CCI

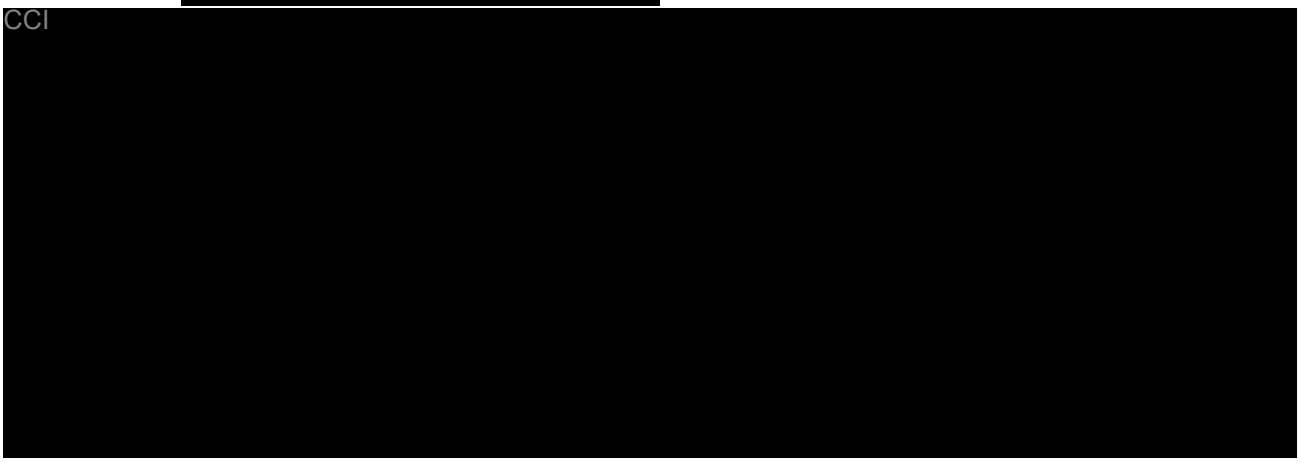
8.6.2.4 CCI

CCI



8.6.2.5 CCI

CCI



8.6.2.6 CCI

CCI

CCI

8.6.2.7 CCI

CCI

8.6.2.8 CCI

CCI

[redacted]

8.6.2.9 CCI

CCI

[redacted]

8.6.2.10 CCI

CCI

[redacted]

8.6.2.11 CCI

CCI

[redacted]

8.7 CCI

CCI

8.8 Other Assessments

8.8.1 Patient-reported Outcomes

"PRO" is an umbrella term referring to all outcomes and symptoms that are directly reported by the participant. Patient-reported outcomes (PROs) have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PROs will be administered in this study: European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30 v3; core questionnaire) and EORTC 13-item Lung Cancer Quality of Life Questionnaire (QLQ-LC13; lung cancer module) (see Appendix G).

The PRO instruments will be completed by the participants using a handheld electronic device (ePRO). All assessments should be completed without assistance from anyone according to the assessment schedules (see Section 1.3). It takes approximately 30 minutes for participants to complete the questionnaires; therefore, the burden to the participant is moderate. Paper may be used as a back up in the event that the electronic device cannot be used.

8.8.1.1 EORTC QLQ-C30

The EORTC QLQ-C30 v3 questionnaire is included for the purpose of assessing health-related quality of life (QoL), and is a well-established measure of health-related QoL/health status and commonly used as an endpoint in cancer clinical studies. The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 6 individual items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global measure of health status (see Appendix G). The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al, 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, each of the function scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the

global health status and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

8.8.1.2 EORTC QLQ-LC13

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

8.8.2 Administration of the Patient-reported Outcome Questionnaires

Participants will complete the PRO assessments by using ePRO during clinic visits at the beginning of the visit. The assessment should be provided first, and should be completed before the participant sees the investigator or is aware of disease response.

Each center must allocate the responsibility for the administration of the PRO instruments to a specific individual (e.g., a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed on the days specified in the SoAs (Section 1.3). The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.

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

- It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid biasing the participant's responses to the questions.
- PRO questionnaires must be completed in private by the participant.
- Participants should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is confidential. Therefore, if the participant has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the participant on how to use the ePRO device using the materials and training provided with the ePRO device. The research nurse or appointed site staff must remind participants that there are no right or wrong answers and avoid introducing bias by not clarifying items. The participant should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.

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

9 STATISTICAL CONSIDERATIONS

On 14 December 2021, AstraZeneca took the decision to terminate enrolment for this study due to the evolving benefit risk profile of AZD2811 that does not support further development for the first-line treatment of patients with extensive stage small-cell lung cancer. Patients already enrolled in the study were able to continue to receive study treatment.

As a result of this decision, the originally intended statistical analyses will be streamlined with respect to efficacy data and the focus of the abbreviated CSR will be on reporting safety data in full. Full details of the analyses will be given in the SAP. Sections from CSP v8.0 are retained below for reference, with some modifications and additional high-level descriptions of changes as applicable.

9.1 Of note, no interim analyses, primary analysis or exploratory external controls analysis will be carried out and the study will proceed to final analysis, based upon which the abbreviated CSR will be written. As a result of the early termination, the DCO for the final analysis in this study is planned for 18 June 2022.Statistical Hypotheses

The study is single arm, so there will be no formal statistical hypotheses. The analysis for the study will be descriptive.

9.2 Sample Size Determination

As a result of the decision on 14 December 2021 to terminate enrolment for this study, no interim or primary analyses will be conducted and the study will proceed to final analysis, based upon which the CSR will be written. The DCO for the final analysis is planned for 18 June 2022. Details of the originally intended sample size and planned analyses are retained below for reference. Note that as of CSP v8.0 the starting dose of AZD2811 in the maintenance phase was reduced to CCI. Due to early termination of enrolment, CSPv8 was never implemented and no new pts started treatment with AZD2811; all new patients transitioning into the maintenance phase were treated with durvalumab monotherapy.

Approximately 100 eligible participants will be assigned study treatment into the induction phase of the study. At the end of the induction phase, those participants who achieve CR, PR, or SD according to RECIST v1.1 will enter the maintenance phase. A minimum of 80 evaluable participants is required for the maintenance phase. To achieve this, additional participants may need to be recruited into the induction phase.

From CSP v8.0 onwards, the starting dose of AZD2811 in the maintenance phase was CCI, the study sought to achieve 80 evaluable participants on that starting dose.

The primary efficacy endpoint is a landmark analysis of the proportion of participants who are APF12 and who have not progressed during EP-durvalumab based induction therapy. The primary analysis will be triggered when a minimum of 80 evaluable participants have had the opportunity to be on the study for approximately 52 weeks + 1 week from the first dose of study therapy in the induction phase. The proportion APF12 and 95% CI will be summarized using the Kaplan-Meier estimate. Based on decision framework (Frewer et al, 2016) with a target value (Senovilla et al) of CCI and a lower reference value (LRV) of CCI, the sample size will permit demonstration of exceeding a CCI landmark PFS at 12 months with 80% probability if the observed landmark PFS at 12 months is at least CCI at the primary analysis.

Two administrative interim analyses will be carried out as described in Section 9.5.

The DCO for the final CSR analysis will occur approximately 18 months following the last participant's first dose, unless the study is terminated based on any of the reasons in Section 4.4.

Enrolled/screened	Estimated 185 participants
Assigned to study intervention	Estimated 130 participants
Evaluable participants	Estimated 90 participants [a]

[a] 80 evaluable at CCI AZD2811 starting maintenance dose.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered "screen failures", unless otherwise specified by the protocol. "Assigned" means that a participant has completed the screening period and has received at least one dose of study treatment.

9.3 Populations for Analyses

The originally planned study populations are defined in Table 23, however, from CSP v9.0 onwards the three analysis sets pertaining to 'Evaluable' participants will not be defined for the abbreviated CSR as they are no longer required for efficacy analyses.

Table 23 Populations for Analysis

Population/Analysis set	Description
Enrolled/screened	All participants who sign the informed consent form
Assigned to study intervention	All participants assigned a study intervention
Evaluable	All participants who entered the maintenance phase and who received at least one dose/have been exposed to any AZD2811 + durvalumab
Evaluable for objective response induction phase	Dosed participants in the induction phase who had measurable disease at baseline
Evaluable for objective response maintenance phase	Dosed participants who entered the maintenance phase, received at least one dose of AZD2811 + durvalumab on Cycle 5 Day 1, and who had measurable disease at baseline
Pharmacokinetics	All participants who received at least one dose of AZD2811 + durvalumab with at least one reportable concentration
Biomarker	All participants who had a baseline biopsy assessment
Safety	All participants who received at least one dose/have been exposed to any study intervention

9.4 Statistical Analyses

Analyses will be performed by Covance under the direction of Oncology Biometrics, AstraZeneca. The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. Given the decision on 14 December 2021 to terminate enrolment, the abbreviated CSR will focus on reporting of safety endpoints as there were were too few patients who received AZD2811 in combination with durvalumab (9 patients) to give meaningful efficacy analyses. Therefore, the efficacy analyses will be streamlined and this will be fully documented in the SAP. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

The main aims of the study are to assess the efficacy, safety, and tolerability of the study intervention in participants who entered the maintenance phase with ES-SCLC.

All analyses will be descriptive, including summaries from Kaplan-Meier curves. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles (as applicable), minimum, and maximum. Log-transformed

data will include geometric mean, geometric standard deviation, and coefficient of variation (CV). Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the relevant analysis.

The summaries, where applicable, will be presented by the following: All participants, participants who only entered the induction phase, and participants who entered the induction and maintenance phase, unless otherwise specified.

From CSP v8.0 onwards, the starting dose of AZD2811 in the maintenance phase was intended to be [redacted], and the study would therefore report efficacy and safety by maintenance phase starting dose of AZD2811 as applicable. Due to early termination of enrolment, CSPv8 was never implemented and no new pts started treatment with AZD2811; all new patients transitioning into the maintenance phase were treated with durvalumab monotherapy. Further details will be provided in the SAP.

Baseline will be the last non-missing value obtained prior to the first dose/administration of study intervention in the induction phase, and any information taken after first dose/administration of study intervention in the induction phase is regarded as post-baseline information. All analyses will use this baseline unless otherwise specified.

An exploratory analysis using external control data will be conducted to compare AZD2811 + durvalumab to durvalumab from the CASPIAN study and will be reported outside of the CSR.

Induction Phase

The induction phase will be from the first dose of platinum-based induction therapy (cisplatin or carboplatin plus etoposide) + durvalumab until the first dose of AZD2811 + durvalumab in the maintenance phase.

Maintenance Phase

At the end of the induction phase, participants will be assessed for disease progression per RECIST v1.1. All participants who have not progressed will be treated with AZD2811 + durvalumab or durvalumab monotherapy as maintenance therapy until confirmed radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Follow-up Period

Period from participant's last dose of any study intervention until end of study.

Demographic data

Characteristics of the participants, including medical history and disease characteristics at baseline, will be listed for each participant and summarized where appropriate.

Exposure

Exposure to study intervention, ie, total amount of study drug received, will be listed for all participants.

Total treatment duration will be summarized by the following: Mean, standard deviation, minimum, maximum, median, and number of observations. In addition, the number and percentages of participants with at least one dose interruption and at least one dose reduction will be presented separately for the planned length of Cycle 1, defined as CCI, and for any time following this initial phase of study. The number of cycles of each study drug will be summarized. Participants are counted as receiving a cycle of study drug as soon as any infusion has started in that cycle.

Dose intensity data will be summarized using medians and quartiles, as well as the minimum and maximum values.

9.4.2 Efficacy

From CSP v8.0 onwards, the starting dose of AZD2811 in the maintenance phase was CCI, the study will therefore primarily report efficacy for the CCI AZD2811 dose. Further sensitivity analyses will be defined in the SAP.

From CSP v9.0 onwards, study enrolment has been terminated and the study will proceed to final analysis and an abbreviated CSR. As a result of this, efficacy analyses will be streamlined as there were too few patients who received AZD2811 in combination with durvalumab (9 patients) to give meaningful analyses.

Sections below containing original plans for reporting efficacy are retained for reference but notable changes will include:

- No summaries of efficacy data will be provided, with the exception of PK, and selected efficacy data will be listed only.
- DoR, PFS2, PRO and breakthrough pain therapy endpoints will no longer be reported in the abbreviated CSR.

Full details of planned efficacy analyses will be documented in the SAP.

9.4.2.1 Primary Endpoint(s)

The primary efficacy endpoint is landmark PFS APF12, where PFS is defined as the time from the first dose of study intervention in the induction phase until objective disease progression (as assessed by the investigator per RECIST v1.1) or death from any cause, whichever comes first. The primary endpoint will only be summarized for participants who entered the maintenance phase and received CCI AZD2811 + durvalumab on CCI Day 1 and includes all data from the first dose of study intervention in the induction phase.

9.4.2.2 Secondary Endpoints

The secondary efficacy endpoints include landmark OS12, OS15, OS18, landmark PFS APF6 and APF9, and OS, PFS, ORR, PK, and health-related QoL. Unless specified otherwise, the secondary endpoints will only be summarized for participants who receive CCI AZD2811 + durvalumab in the maintenance phase and include all data from first dose of study intervention in the induction phase. The ORR will be presented for all participants in the induction phase. The ORR will also be presented for all participants who received AZD2811 + durvalumab in the maintenance phase and include all data from first dose of study intervention in the induction phase.

9.4.2.3 CCI

CCI

Progression-free survival

The PFS analysis is for those participants who entered the maintenance phase and received AZD2811 + durvalumab on CCI Day 1.

Progression-free survival is defined as the time interval from the first dose of study intervention in the induction phase until the date of objective disease progression or death (by any cause, in the absence of progression) regardless of whether the participant withdraws from treatment or received another anticancer therapy prior to progression. Participants who have not progressed (defined as CR, PR, or SD by RECIST v1.1) at the time of analysis will be censored at the time of the last evaluable RECIST v1.1 assessment.

However, if the participant progresses or dies after 2 or more consecutively missed radiologic visits, the participant will be censored at the time of the last evaluable RECIST v1.1 assessment prior to the 2 missed visits. Note: A NE visit is not considered as a missed visit. If

the participant is NE post-baseline RECIST v.1.1, they will be censored at Day 1 unless they die within 2 visits of baseline (in which case, their date of death will be used).

Progression-free survival will be derived based on scan/assessment dates, not the scheduled visit dates. If RECIST v1.1 assessments contributing toward a particular visit are performed on different dates, then the date of progression will be determined based on the earliest of the dates of the component that triggered the progression. With regard to censoring, a participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

Summaries (number of events, medians, proportion, and 95% CI for progression free at fixed time points using the Kaplan-Meier estimate) and Kaplan-Meier plots will be provided. A 2-sided 95% CI of the median PFS will be produced in addition to the 25th and 75th percentiles. The fixed time points may include the following: 6 weeks, 12 weeks, 18 weeks, 24 weeks, 36 weeks, 44 weeks, and 52 weeks. Other fixed time points may be included and will be documented in the SAP.

The landmark of the proportion of participants APF6, APF9, and APF12 will be defined as the Kaplan-Meier estimate of PFS (per RECIST v1.1 as assessed using site investigator assessments) at 24 + 1 weeks, 36 + 1 weeks, and 52 + 1 weeks to align with the planned scan schedule and allowing for a 1-week window. Confidence intervals will also be presented.

Time from start of study therapy in the induction phase to second progression

The analysis of the exploratory endpoint PFS2 is for those participants who entered the maintenance phase.

The exploratory endpoint PFS2 will be defined as the time from the start of study therapy in the induction phase to the earliest of the progression event subsequent to that used for the PFS endpoint, or death. The date of PFS2 will be recorded by the investigator in the eCRF and defined according to local standard clinical practice, and may involve any of the following: Objective radiological imaging, symptomatic progression, or death. The site will be asked whether the participant has had a second progression event on a regular basis following the first progression event used for the primary variable PFS (the first progression) and the status is recorded. Participants alive and for whom a second disease progression has not been observed will be censored at the last time known to be alive and without a second disease progression, and is censored at the latest of the PFS or PFS2 assessment date if the participant has not had a second progression or has died.

Overall survival

The OS analysis is for those participants who entered the maintenance phase and received CCI AZD2811 + durvalumab on CCI Day 1. For the participants who do not enter the maintenance phase, their survival data will only be listed.

Overall survival is defined as the time from the date of first dose of study intervention in the induction phase until death due to any cause, regardless of whether the participant withdraws from study therapy or received another anticancer therapy. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Note: Survival calls will be made in the week following the date of DCO for the analysis and, if participants are confirmed to be alive or if the death date is after the DCO date, these participants will be censored at the date of DCO.

Summaries (number of events, medians, proportion, and 95% CI for participants alive at fixed time points using the Kaplan-Meier estimate) and Kaplan-Meier plots will be provided. A 2-sided 95% CI of the median OS will be produced in addition to the 25th and 75th percentiles. The fixed time points may include the following: 6 months, 9 months, 12 months, 15 months, and 18 months. Other fixed time points may be included and will be documented in the SAP.

The landmark of the proportion of participants alive: OS12, OS15, and OS18, will be defined as the Kaplan-Meier estimate of OS at 12, 15, and 18 months, respectively. Confidence intervals will also be presented.

Tumor response

Tumor response data will be summarized for dosed participants with measurable disease at baseline, and separately for dosed participants with measurable or non-measurable disease at baseline.

Tumor response data will be listed using the following response categories: CR, PR, SD, Non-CR/Non-PD, PD, and NE.

Objective response rate is defined as the percentage of participants with confirmed objective response (CR or PR). It will be based on a subset of all treated participants with measurable disease at baseline, per the site investigator. A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Also, only data obtained before the start of subsequent anticancer treatment (excluding radiotherapy) will be included. Therefore, both visits contributing to a confirmed response must be prior to progression and prior to subsequent anticancer treatment.

Summaries will be produced that present the number and percentage of participants with a tumor response (CR/PR). The ORR will be presented with a 2-sided 95% CI using the

Clopper-Pearson (exact probability) method. Participants who have missing overall response assessments at all visits will be considered as non-responders, and will therefore be counted in the denominator of ORR. The ORR will be summarized for all participants in the induction phase and, in addition, ORR will be summarized for those participants who were in the maintenance phase.

Waterfall plots (bar plots) and spider plots (individual line plots of percent change from baseline over time), indicating the percentage change from baseline in sum of the diameters of the TLs, will be produced. Specifically, these plots will be based on the sum of diameters as entered in the database, including no adjustment as a function of tumor response in the case of participants with lymph node regression.

Duration of Response

The DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until date of first documented progression or death (by any cause, in the absence of disease progression). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing toward the first visit that was PR or CR that was subsequently confirmed.

The DoR will be analyzed in the same manner as PFS, if the number of participants with DoR allows. In addition, Swimmer plots will be produced.

If a participant does not progress following a response, then their DoR will use the PFS censoring date at the date at which that participant is censored for DoR.

9.4.3 Patient-reported outcomes

From CSP v9.0 onwards, study enrolment has been terminated and the study will proceed to an abbreviated CSR. As a result of this, efficacy analyses will be streamlined and PRO data will no longer be reported.

Patient-reported outcome questionnaires will be assessed using the EORTC QLQ-C30 with the QLQ-LC13 module (health-related QoL and lung cancer-specific symptoms). For PRO symptoms and health-related QoL endpoints, the main concepts of interest are based on the CASPIAN study. In the CASPIAN study, the main concepts of interest were identified using a literature review and detailed qualitative interviews with SCLC patients and clinicians. The key symptoms were: Cough, hemoptysis, dyspnea, chest pain, insomnia, fatigue, and appetite loss. Therefore, these key SCLC symptoms will be identified as primary measures of interest. In addition, physical functioning and overall health status domains of the EORTC QLQ-C30 are prespecified endpoints of interest.

Summary statistics for mean score, standard deviation, median, and range will be presented by visits until there are less than one third of participants with evaluable data. Box plots may also be presented.

Time to symptom and function/health-related QoL deterioration will be analyzed for each of the symptom scales/items, function scales, and global health status/QoL in EORTC QLQ-C30 and QLQ-LC13. This will be assessed using the same methods as for the primary analysis.

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

Further details on how these data will be analyzed will be detailed and prespecified in the SAP.

9.4.3.1 EORTC QLQ-C30

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

9.4.3.2 EORTC QLQ-LC13

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

9.4.4 Safety

From CSP v9.0 onwards, study enrolment has been terminated and the study will proceed to an abbreviated CSR. The abbreviated CSR will present a full safety report and as such the analysis of safety endpoints will remain largely unchanged. Any changes to the planned analyses below will be fully described in the SAP and will be limited to instances where, in light of the early termination of enrolment, listings of specific data points are more appropriate than summaries.

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, physical examination, and exposure. These will be collected for all participants. Data from all cycles of study intervention will be combined in the presentation of safety data, along with summaries of the induction phase and the maintenance phase unless

otherwise specified. Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics. Analyses will be presented for the overall study and separately for the induction and maintenance phases.

From CSP v8.0 onwards, the patients who were transitioned onto the maintenance phase received CCI of AZD2811, and the study will therefore report efficacy and safety by maintenance phase starting dose of AZD2811 as applicable. Further details will be provided in the SAP. In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study intervention in the induction phase. Details will be described in the SAP.

Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for application by AstraZeneca/designee.

"On treatment" will be defined as assessments between date of start dose of study intervention in the induction phase and 90 days following discontinuation of study intervention (90 days after the last dose of AZD2811 + durvalumab or durvalumab + EP). For AEs, on treatment (or treatment-emergent AEs [TEAEs]), will be defined as any AEs that started after dosing or prior to dosing and which worsen following exposure to study intervention.

Adverse events observed up until 90 days following discontinuation of study intervention (ie, 90 days after the last dose of AZD2811 + durvalumab or durvalumab + EP) or until the initiation of the first subsequent therapy following discontinuation of study intervention (whichever occurs first) will be used for reporting of AE summary tables. This will more accurately depict AEs attributable to study treatment only because a number of AEs up to 90 days following discontinuation of study intervention are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of study intervention (ie, without taking subsequent therapy into account).

Any events in this phase that occur after a participant has received further therapy for cancer (following discontinuation of study intervention) will be flagged in the data listings.

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

Adverse events will be presented by MedDRA system organ class, MedDRA preferred term, and CTCAE grade, including the number and percentage of participants reporting at least one event, number of events, and exposure adjusted rates, where appropriate.

An overview of AEs will be presented for each phase, including the number and percentage of participants with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention.

Separate AE tables will be provided, taking into consideration the relationship with study intervention assessed by the investigator, CTCAE grade, seriousness, death, and events leading to discontinuation of study intervention, as well as other action taken related to study intervention.

Dose-limiting toxicities will be displayed in the listing for the DLT-evaluable participant population.

Full details of AE analyses will be provided in the SAP.

Treatment Emergent

The following events are considered treatment emergent:

- Adverse events with an onset date on or after the first dose of study intervention
- Worsening of pre-existing events on or after the first dose of study intervention

Clinical Laboratory Safety Assessments

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Shifts from baseline to maximum value during treatment will be evaluated for urinalysis.

Vital Signs and Physical Examination

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover number of participants, mean, standard deviation, minimum, quartile 1, median, quartile 3, and maximum. Frequency tables cover number and percentage of participants in the respective category.

The baseline value will be the latest result obtained prior to the start of study intervention in the induction phase.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and absolute change from baseline.

Changes in vital signs will be examined at each visit. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented.

Details of vital sign analyses will be provided in the SAP.

All individual physical examination and targeted physical examination data will be listed only.

ECG

For the change from baseline summaries for ECG, the baseline value will be the latest result obtained prior to the start of study intervention in the induction phase.

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

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

9.4.4.1 Other Safety Endpoint(s)

The ECOG PS will be listed.

The number of participants who stop break-through pain therapy during maintenance therapy will also be summarized.

9.4.5 Other Analyses

The PK, pharmacodynamic, demographic, safety, and tumor response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or population PK-pharmacodynamic methods. The results of such analyses will be reported separately from the main CSR.

9.4.6 CCI

CCI

[redacted]

9.4.7 Pharmacokinetic Analyses

For each analyte, whole blood or serum concentrations for each scheduled time point will be summarized by visit using appropriate descriptive statistics. Protocol scheduled times will be used to present the PK concentration summary tables and corresponding geometric mean concentration-time figures. Additional details for the handling of non-quantifiable concentrations will be included in the SAP.

- The geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)

- gmean ± geometric standard deviation (gmean + gstandard deviation and gmean – gstandard deviation), which are calculated as exp(μ ± s)
- CV, calculated as 100 sqrt (exp[s^2]-1), where s is the standard deviation of the data on a log scale
- gmean ± standard deviation (calculated as exp[μ ± s])
- Arithmetic mean, calculated using untransformed data
- Standard deviation, calculated using untransformed data
- Minimum
- Maximum
- Number of observations
- Number of participants below lower limit of quantification

9.5 Interim Analyses

Two interim analyses were originally planned. However, due to the decision on 14 December 2021 to terminate enrolment for this study these will no longer be carried out. Details of the originally planned interim analyses are retained below.

These are administrative interim analyses, which is an administrative review of the data to trigger additional development work for AZD2811; as such, no modifications will be made to the current study, and the study will continue as planned. The review will consist of safety and tolerability outputs, including SAEs, TEAEs, exposure, and the efficacy endpoints of APF6 and APF9 for the first and second interim analysis, respectively, including other important efficacy endpoints. At the second interim analysis the landmark PFS APF12 will also be assessed, it is anticipated that approximately 50 participants will have had the opportunity to be on the study for at least 12 months from the first dose of study therapy in the induction phase at the timing of the second interim analysis.

The first administrative interim analysis will be based on landmark PFS APF6 in participants who have not progressed during EP-durvalumab based induction therapy. The analysis will be triggered when a minimum of 80 evaluable participants have received AZD2811 + durvalumab and have had the opportunity to be on the study for approximately 24 weeks + 1 week from the start of induction. Based on decision framework (Frewer et al, 2016) with a TV (Senovilla et al, 2012) of CCI and a LRV of CCI the sample size will permit demonstration of exceeding a CCI landmark PFS APF6 with CCI probability if the observed landmark PFS APF6 is at least CCI at this interim analysis.

From CSP v8.0 onwards, the starting dose of AZD2811 in the maintenance phase will be CCI, all the interim analyses of efficacy will focus on the CCI dose.

The second administrative interim analysis will be based on landmark PFS APF9 in participants who have not progressed during EP-durvalumab based induction therapy. The analysis will be triggered when a minimum of 80 evaluable participants have received AZD2811 + durvalumab and have had the opportunity to be on the study for approximately 36 weeks + 1 week from the start of induction. Based on decision framework (Frewer et al, 2016) with a TV of CCI and a LRV of CCI, the sample size will permit demonstration of exceeding a CCI landmark PFS APF9 with CCI probability if the observed landmark PFS APF9 is at least CCI at this interim analysis. At the second interim analysis, the landmark PFS APF12 will also be assessed, as it is anticipated that approximately 50 participants will have had the opportunity to be on the study for at least 12 months from the first dose of study therapy in the induction phase at the timing of the second interim analysis. Based on decision framework (Frewer et al, 2016) with a TV of CCI and a LRV of CCI, the sample size will permit demonstration of exceeding a CCI landmark PFS APF12 with CCI probability if the observed landmark PFS APF12 is at least CCI at this interim analysis.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee

A SRC will be used to assess the participants in the safety run-in part of the maintenance phase of the study. The SRC structure is detailed in Appendix A 5

10 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 International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (e.g., 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 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 participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization (CRO), but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of Code of Federal Regulations number 21 (21 CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the Sponsor of a serious adverse event (SAE) is essential so that legal obligations and ethical responsibilities toward 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 utilizing 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.
  - European MDR 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB or other documents and will notify the IRB/IEC, if appropriate according to local requirements.

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 one 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 participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants 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. Participants or their legally authorized representative, defined as "an individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial", per ICH GCP E6(R2), 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 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 participant 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.
- Participants 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 participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date. A participant who is re-treated following relapse will need to be re-consented.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information, which would make the participant identifiable, will not be transferred.
- The participant 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 and use of their data must also be explained to the participant in the informed consent.
- The participant 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

A Safety Review Committee (SRC) will review the data from the safety run-in of the maintenance phase.

The SRC will consist of:

- Study Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from the investigational sites

In addition, one other physician from the following may be invited:

- Sponsor Global Safety Physician or Medical Science Director

The study clinical pharmacologist, study statistician, patient safety scientist, clinical project manager, and other experts may also be invited as appropriate. Further internal or external experts may be consulted by the SRC as necessary. The global safety physician or delegate should always be present at the SRC.

See the Safety Review Committee Charter for further details.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the electronic Case Report Form (eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH and 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 or discontinuation

of the trial; or at least 2 years after local market approval for the indication for which it is being investigated; or, if no market approval is filed or is not approved for such indication, at least 2 years after the investigation is discontinued with local authorities; or per local regulations or institutional policies, whichever retention period is longer. 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 participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF 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.
- Definition of what constitutes source data can be found in the Clinical Study Agreement.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site activated and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant(s) and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 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 multicenter studies only in their entirety and not as individual site data. In this case, a co-ordinating 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 Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study participant 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 (e.g., an abnormal laboratory finding), symptom (e.g., nausea, chest pain), or disease temporarily 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 nonserious 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 intervention has been administered.

B 2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is **not** the tumor for which entry into the study is a criterion and that is being treated by the investigational product under study, and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors 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 tumor.

Life-threatening

'Life-threatening' means that the participant 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

participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g., 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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment 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 participant 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 judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous 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 (e.g., neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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.

The grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) latest version 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 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 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 participant 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 no available facts or arguments to suggest a causal relationship, 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 4 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 intervention that either causes harm to the participant or has the potential to cause harm to the participant.

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

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

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

- Drug name confusion
- Dispensing error, e.g., medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, e.g., wrong route or wrong site of administration
- Drug not taken as indicated, e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, e.g., kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology [IRT]/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during the remainder of the sample lifecycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, is life-threatening, or causes a fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria, which cause disease in humans or both in humans and animals, must be assigned to UN 2814. Infectious substances, which cause disease only in animals, must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

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

Exempt - Substances that do not contain infectious substances or substances that are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D CCI

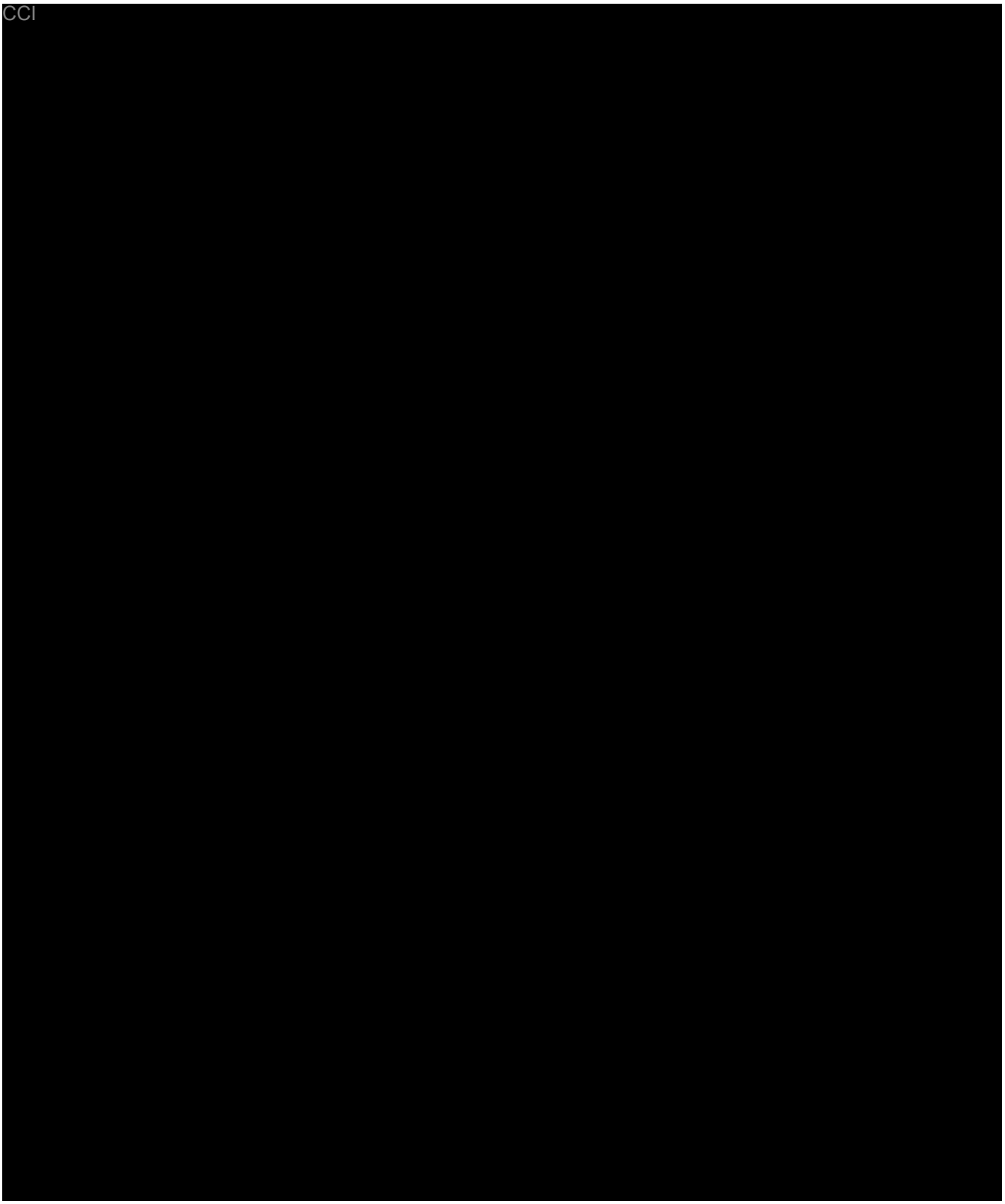
D 1 CCI

CCI

D 2 CCI

CCI

CCI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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 (Veuillen et al, 2012) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant 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 all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine aminotransferase ALT **and/or** elevated total bilirubin (TBL) from a local laboratory.

The investigator will also review adverse event (AE) data (e.g., 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 (Veuillen et al, 2012) criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the investigational product (IP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting serious adverse events (SAEs) and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2\times$ ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

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

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

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 participant 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 participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant 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 participant does meet PHL criteria, the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within one day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For participants who met PHL criteria prior to starting IP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition
- The Study Physician contacts the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing), and ensure the continuous review of data
- Subsequent to this contact, the investigator will:
  - Monitor the participant 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 etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the 3 Liver eCRF modules as information becomes available

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) 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 IP, 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 eCRF
- If the alternative explanation is an AE/SAE: Update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

- 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:

- Provide 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 IP 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 amend 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 Intervention

This section is applicable to participants with liver metastases who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met, the investigator will determine if there has been a **significant change** in the participants' 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 Section E 4.2

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on-study intervention visit.

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

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

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

If **No**: Follow the process described in Section E 4.2 for reporting PHL as an SAE

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

- If there is no significant change, no action is required
- If there is a significant change[#], follow the process described in Section E 4.2 for reporting PHL as an SAE

[#] **A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) 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 Recommended Laboratory Tests

Additional standard chemistry and coagulation tests	Gamma GT (GGT) Lactate dehydrogenase (LDH) Prothrombin time International Ratio (INR)
Viral hepatitis	IgM anti-Hepatitis A Virus Hepatitis B surface antigen Immunoglobulin M (IgM) and Immunoglobulin G (IgG) hepatitis B core antigen (anti-HBc)
	Hepatitis B Virus DNA [a] IgG anti-Hepatitis C Virus (HCV) HCV RNA [b] IgM anti-Hepatitis E Virus (HEV) HEV RNA
Other viral infections	IgM and IgG anti-Cytomegalovirus (CMV) IgM and IgG anti-Herpes Simplex Virus IgM and IgG anti-Epstein Barr Virus
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-liver/kidney microsomal Ab (anti-LKM) Anti-smooth muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 9 References

Aithal et al, 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Clinical Pharmacology and Therapeutics 2011;89(Research Report NN210296):806-15.

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Appendix F Guidelines for Evaluation of Objective Tumor Response Using RECIST v1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

F 1 Introduction

This Appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines (Eisenhauer et al 2009) for this study with regard to investigator assessment of tumor burden, including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiological progression.

F 2 Definition of Measurable, Non-measurable, Target, and Non-target Lesions

Measurable:

A lesion, which can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis[1] diameter of ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis diameter at baseline[2]).
- Truly non-measurable lesions include the following: Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination (manual palpation) that is not measurable by CT or MRI.
- Previously irradiated lesions[3]
- Brain metastasis

[1] The short axis is defined as the longest axis perpendicular to the long axis of the tumor.
[2] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).
[3] Localized post-radiation changes that affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

- Skin lesions assessed by clinical examination

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as target lesions (TLs).

Target Lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline. Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (e.g., adrenal glands), a segmented organ (e.g., liver), or multilobed organ (e.g., lung) is each considered as a single organ.

Non-Target Lesions:

Additional measurable lesions not recorded as TLs and non-measurable lesions (or sites of disease) should be identified as non-target lesions (NTLs) at baseline.

F 3 Imaging Modalities

The same method of assessment on the same imaging technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods of assessment (imaging modalities) to be used for RECIST v1.1 assessment of TLs, NTLs, and new lesions, is provided in Table 24.

Table 24 Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray, Chest X-ray
	Chest X-ray	Bone scan
	Clinical examination	FDG-PET/CT
		Clinical examination
		Ultrasound

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

F 3.1 CT and MRI

Computed tomography and MRI, each preferably with intravenous (IV) contrast, are generally considered to generate the best currently available and reproducible images for measurement of TL, assessment of NTL, and identification of any new lesions.

It is recommended that IV contrast-enhanced CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement (eg, pelvis, brain) should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV MRI contrast of the abdomen is appropriate. In patients with severely compromised renal function, a non-contrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, and scanner across all imaging time points per patient.

F 3.2 Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients who also have other lesions assessable by CT, MRI, or plain X-ray and to identify the presence of new lesions.

F 3.3 X-ray

F 3.3.1 Chest X-ray

Chest X-ray assessment will not be used for assessment of TLs. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

F 3.3.2 Plain X-ray

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

F 3.4 Ultrasound

In this study, ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of true tumor size. Ultrasound examination can, however, be used to identify the presence of new lesions. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

F 3.5 Endoscopy and laparoscopy

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

F 3.6 Tumor markers

Tumor markers on cytological or histological (biopsy) samples will not be used for tumor response assessments as per RECIST v1.1.

F 3.7 Histology and cytology

Histology on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST v1.1.

Results of cytological examination for the neoplastic origin of any effusion (e.g., ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to new lesions or progression of NTLs, respectively.

F 3.8 Isotopic bone scan

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

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan, however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a progressive disease assessment at that time point.

F 3.9 FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[4] not present on baseline or prior FDG-PET scan, or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline or prior FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST v1.1. 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, the CT portion of the PET/CT can be used for RECIST v1.1 tumor assessments. Caution: 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.

F 4 Tumor Response Evaluation

F 4.1 Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including the entire liver and both adrenal glands) must be used at each subsequent

[4] A positive FDG-PET scan lesion should be reported only when uptake is greater than approximately twice that of the surrounding tissue or liver.

follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient (e.g., new lesions at follow-up).

The baseline scan for this study must be done within 21 days prior to Day 1 of Cycle 1 and ideally should be performed as close as possible to the start of investigational product. The patient's diagnostic scan can be used as the baseline scan if it complies with recommended Image Acquisition Guidelines for assessing tumor burden in the chest and abdomen (including liver and adrenal glands) within 28 days prior to Cycle 1 Day 1. The scan performed to confirm eligibility for the maintenance phase must be performed within 1 week prior to CCI .

Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks (Q6W) ± 1 week, for the first 36 weeks (relative to the date of first dose of study intervention in the induction phase; see Section 1.3 and Section 8.1), then every 8 weeks (Q8W) ± 1 week thereafter until objective disease progression as defined by RECIST v1.1 (irrespective of the reason for stopping treatment/or subsequent therapy). It is important to follow the assessment schedule as closely as possible (refer to the SoAs in Table 1, Table 3, and Table 4). Where possible, every effort should be made to schedule the scan within 1 week prior to dosing with AZD2811; scan results **MUST** be reviewed prior to dosing to confirm the absence of disease progression.

For patients who discontinue study drug due to toxicity in the absence of objective progression, objective tumor assessments should be continued Q6W ± 1 week for 36 weeks (relative to the date of Cycle 1 Day 1), then Q8W ± 1 week until confirmed objective disease progression.

Radiographic progression (PD by RECIST v1.1) requires collection of the subsequent scan no earlier than 4 weeks after the prior assessment of PD and no later than the next regularly scheduled imaging visit. In patients receiving study treatment beyond the first RECIST v1.1-defined PD, if progression is not confirmed with the subsequent scan, they may continue on study treatment and continue with imaging assessments on their regular schedule.

If disease progression is suspected, an unscheduled radiological imaging assessment should be performed. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Additional assessments will be performed post objective disease progression for patients remaining on treatment, or until subsequent cancer therapy according to the clinical study protocol.

F 4.2 Target lesions

F 4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special Cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a TL has completely disappeared, the diameter should be recorded as 0 mm for the current and all subsequent scans. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion, and the overall visit assessment will be designated as PD.
- When a TL has had any intervention, e.g., definitive radiotherapy, embolization, surgery, etc., during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form for that time point and in all

subsequent TL assessments (see 'Not evaluable' below). If a TL has been completely removed (surgery) or disappears following an intervention, the diameter should be recorded as 0 mm.

F 4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (Table 25).

Table 25 Evaluation of Target Lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to < 10 mm
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease (SD)	Neither sufficient decrease in sum of diameter to qualify for PR nor sufficient increase to qualify for PD
Progression of disease	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) - this includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (e.g., missing anatomy) or had a lesion intervention at this visit. *Note:* If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

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

F 4.3 Non-target lesions

F 4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the . This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (Table 26).

Table 26 Evaluation of Non-target Lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/non-PD	Persistence of one or more NTL.
Progression	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. *Note:* For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR = Complete response; PR = Partial response; PD = Progressive disease; NE = Not evaluable; NTL = Non-target lesion; TL = Target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

F 4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than a tumor.

If a new lesion is equivocal, e.g., because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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

F 4.5 Symptomatic deterioration

Symptomatic (clinical) deterioration is not a descriptor of an objective response: It is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective radiologic evidence of disease progression at that time should continue to undergo tumor assessments where clinically feasible.

F 4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 27.

Table 27 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete response; NA = Not applicable (relevant when no TLs or NTLs are present at baseline); NE = Not evaluable; NED = No Evidence of Disease (relevant when neither TLs nor NTLs are present at baseline); NTL = Non-target lesion; PD = Progressive disease; PR = Partial response; SD = Stable disease; TL = Target lesion.

F 5 Confirmation of Radiological Progression

A follow-up scan is collected after the initial RECIST v1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD, and the Confirmation of Radiological Progression criteria described below are applied for tumor assessments of this follow-up scan. Patients with radiological PD who

continue to receive study treatment at the discretion of the investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit.

Confirmation of radiological progression guidelines are set for the following reasons:

- For patient management and treatment decisions
- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST v1.1 assessment of PD in order to distinguish pseudoprogression from true radiologic progression.

Confirmation of Radiological Progression Criteria:

Confirmation of radiological progression guidelines are used to evaluate scans subsequent to a prior radiological PD. An immediate prior RECIST v1.1-defined radiologic PD would be considered confirmed if any of the following criteria are met in a subsequent follow-up scan (acquired preferably at the next regularly-scheduled imaging visit but no sooner than 4 weeks after RECIST v1.1-defined PD scan):

- ≥ 20% increase in the sum of diameters of TLs compared with the nadir at 2 consecutive visits, each with an absolute increase of at least 5 mm in sum of diameters compared to nadir (as per RECIST v1.1 definition)
- *and/or* significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point (as per RECIST v1.1 definition)
- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan time point compared with the immediate prior time point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time point)
- *and/or* additional (brand) new unequivocal lesions at the follow-up scan time point (as per RECIST v1.1 definition).

NOTE: In order to have confirmed radiological progression, there should be 2 consecutive assessments meeting the PD definition, the first PD by RECIST v1.1 and the second PD using the confirmation of radiological progression criteria (above). If the first assessment fulfilling the PD definition by RECIST v1.1 is not confirmed, the patient may continue with assessments until the next PD by RECIST v1.1, which will also require a follow-up scan evaluated using the Confirmation of Radiological Progression criteria. **If the first PD (by RECIST v1.1) is not confirmed by the immediate next scan, then the investigator should not change the PD assessment of the first scan.**

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until objective disease progression.

F 6 Central Review

All images will be collected, quality checked, and stored centrally by an Imaging Contract Research Organization (CRO) appointed by AstraZeneca. Guidelines for image acquisition, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document.

F 7 Specifications for Radiological Imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

If specified, all images will be collected, quality checked, and stored centrally by the imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely upon the local assessments conducted by the investigator.

F 7.1 CT Scan

Computed tomography scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomical region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST v1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

F 7.1.1 Anatomic coverage

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

F 7.1.2 Contrast administration

Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease, and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT thoracic (Fry et al, 2016) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed, then CT without IV contrast is an option for the thorax and abdomen (and pelvis examination). For brain imaging, MRI with IV contrast is the preferred method.

F 7.1.3 Slice thickness and reconstruction interval

It is recommended that CT scans be performed at 5 mm contiguous slice thickness, and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

F 7.2 MRI Scan

Magnetic resonance imaging has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies, e.g., neck) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression, and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. Computed tomography of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, and breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

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Appendix G Patient-Reported Outcomes: EORTC QLQ-C30, EORTC QLQ-LC13

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

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 (e.g., during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants 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 notification from the Sponsor, and instructions on how to perform these procedures will be provided at the time of implementation.

H 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants 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 H 2 to H 5. Local and regional regulations and/or guidelines regarding reconsent of study participants 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 participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Rescreening of Participants to Reconfirm Study Eligibility

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

In addition, during study disruption, there may be a delay between confirming eligibility of a participant and either enrollment into the study or commencing of dosing with investigational product. If this delay is outside the screening window specified in Section 1.3, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.5. The procedures detailed in Section 1.3 must be undertaken to confirm eligibility using the same enrollment number as previously assigned to the participant.

H 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified Health Care Professional (HCP) from the study site or third-party vendor (TPV) service will visit the participant's home or other 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 Clinical Study Protocol. If applicable, assessments will be performed according to a revised Schedule of Activities.

H 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants 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 participants will allow adverse events, concomitant medication, etc to be reported and documented. If applicable, safety procedures and blood sample collection will be performed according to the revised SoA.

H 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service, or by the participants themselves, e.g., patient reported outcomes.

H 6 COVID-19 Risk Assessment

The safety of participants 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 participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants 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 H 9). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant 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, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2, Exclusion Criterion 1).

H 7 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section H 10 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab. The risk-benefit assessment should be carefully considered for each participant 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 participants 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.

H 8 New Participant Enrolment

Study sites may continue to recruit new participants 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 participants 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 Criterion 1 (see CSP Section 5.2), participants with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID 19) should not be included for study participation.

H 9 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product 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

H 10 Ongoing Participants

Participants receiving study intervention 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 intervention should be interrupted until such assessments can be completed.

H 10.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention 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 TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention 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.

H 10.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention 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/tremelimumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

H 10.3 Restarting Study Intervention

Study intervention 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.

H 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 participants 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.

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Appendix I Abbreviations

Abbreviation or special term	Explanation
1L	first line
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
ANC	absolute neutrophil count
APF6	proportion of participants alive and progression free at 6 months from treatment assignment(ie, PFS rate at 6 months)
APF9	proportion of participants alive and progression free at 9 months from treatment assignment (ie, PFS rate at 9 months)
APF12	proportion of participants alive and progression free at 12 months from treatment assignment (ie, PFS rate at 12 months)
AST	aspartate aminotransferase/transaminase
CD	cluster of differentiation
CCI	
CI	confidence interval
CL	clearance
CNS	central nervous system
CR	complete response
CRO	Contract Research Organization
CRP	C-reactive protein
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CCI	
CTCAE	Common Terminology Criteria for Adverse Events
CCI	
DILI	Drug Induced Liver Injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
DUS	disease under study
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Appendix I Abbreviations

Abbreviation or special term	Explanation
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOT	end of treatment
EP	etoposide and platinum-based chemotherapy
ePRO	electronic handheld device for participants to record patient-reported outcomes
ES-SCLC	extensive-stage small cell lung cancer
EU	European Union
FDA	United States Food and Drug Administration
CCI	[redacted]
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	Health Care Professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hy's Law
HRCT	high-resolution computed tomography
IB	Investigator's Brochure
ILD	interstitial lung disease
IXRS	interactive voice/web response system
IATA	International Airline Transportation Association
ICF	informed consent form
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
LRV	lower reference value
mAb	monoclonal antibody

Appendix I Abbreviations

Abbreviation or special term	Explanation
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
NP	nanoparticle
NTL	non-target lesion
ORR	objective response rate
OS	overall survival
OS12, OS15, OS18	participants alive at 12, 15, 18 months
PD	progressive disease
PD-1	programmed cell death-protein 1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PEG	polyethylene glycol
PFS	progression-free survival
PFS2	progression-free survival after subsequent anticancer therapy
PHL	Potential Hy's Law
PI	Principal Investigator
PK	pharmacokinetic(s)
PNS	paraneoplastic syndrome
PR	partial response
PRO	patient-reported outcomes
PS	performance status
CCI	[redacted]
Q6W	every 6 weeks
Q8W	every 8 weeks
QLQ-C30	30-item Core Quality of Life Questionnaire
QLQ-LC13	13-item Lung Cancer Quality of Life Questionnaire
QoL	quality of life
QTcF	Fridericia's Correction Formula
RECIST	Response Evaluation Criteria in Solid Tumors
RR	respiratory rate
RTSM	Randomization and Trial Supply Management

Appendix I Abbreviations

Abbreviation or special term	Explanation
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small-cell lung cancer
SD	stable disease
SoA	Schedule of Activities
SOC	standard of care
SpO2	saturation of peripheral oxygen
SRC	Safety Review Committee
T_3	triiodothyronine
T_4	thyroxine
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TL	target lesion
CCI	[redacted]
TMG	toxicity management guidelines
TPV	third-party vendor
TV	target value
ULN	upper limit of normal
WHO	World Health Organization

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.