Statistical Analysis Plan	
Study Code	D419BR00018
Edition Number	2.0
Date	6 Apr 2022

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

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LIST OF ABBREVIATIONS

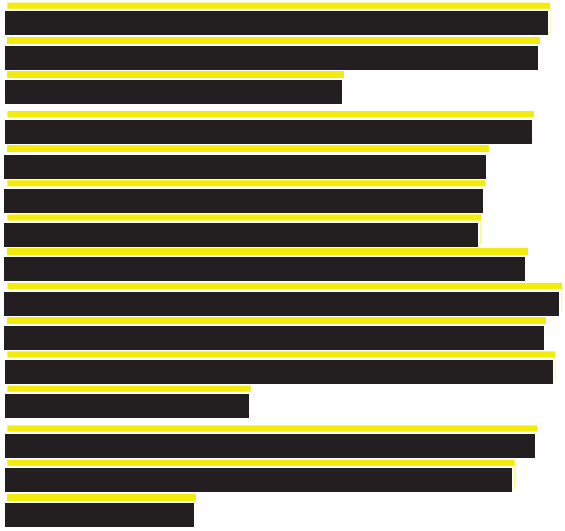
Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American joint committee on cancer
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APF	Alive and progression free
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BMI	Body mass index
CD	Cluster of differentiation
CI	Confidence interval
CL	Calculated creatinine clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
C_{min}	Minimum plasma concentration
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DBP	Diastolic blood pressure
DCO	Data cut −off
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation or special term	Explanation
EGFR	Epidermal growth factor receptor
ES-SCLC	Extensive stage small-cell lung cancer
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Hazard ratio
IASLC	International Association for the Study of Lung Cancer
IC	Immune cell
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IP	Investigational product
IO	Immuno-oncology
LLN	Lower limit of normal
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not evaluable
nmiss	No. of missing patients
no.	Number
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PCI	Prophylactic cranial irradiation
PK	Pharmacokinetic(s)
PLT	Platelet
PR	Partial response

Abbreviation or special term	Explanation
PT	Preferred term
q3w	Every 3 weeks
q4w	Every 4 weeks
QC	Quality control
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SBP	Systolic blood pressure
SCLC	Small-cell lung cancer
SD	Stable disease
SI	International system
SoC	Standard of care
SOC	System organ class
SS	Safety set
Std	Standard deviation
TBil	Total bilirubin
TC	Tumor cells
TFL	Table, figure and listing
TL	Target lesion
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WNL	Within normal limits

AMENDMENT HISTORY

Date	Category*: Change refers to	Description of change	In line with the CSP?	Rationale
2 Apr 2022	Other Page 2	Statisticians from Tigermed were added on signature pages. AZ statistician was changed from Wenhan Jiang to Li Luo. AZ medical advisor was changed from Min Gao to Ziyi Huang. AZ global product statistician were added on signature page.	NA	Team member change in AZ. Tigermed SOP require signature of statistician from Tigermed for SAP.
2 Apr 2022	Other Section 2.2, page 13	4 general categories of IPD were deleted and replaced by the sentence 'Several IPDs could be identified with programming to assist locating potential IPDs.'	Yes	The specification of IPD will be written in the external file of PD log but not in SAP.
2 Apr 2022	Derivation of primary or secondary endpoints Section 3.2.3, page 17	'(2 x 6 weeks for tumor assessments + 2 x 2 weeks for permitted visit window)' were added.	Yes	This sentence was added to explain clearly what the 2 visit after baseline means.
2 Apr 2022	Derivation of primary or secondary endpoints Section 3.2.3, page 18	In table 4, 'Patients without PD and death' was replaced by 'Patients without PD and death but had post-treatment tumor assessment'.	Yes	To be more clear.
2 Apr 2022	Derivation of primary or secondary endpoints Section 3.2.3, page 18	In table 4, for the case of patient died after treatment without tumor assessment, 12 weeks was modified to 16 weeks.	Yes	Since 2 x 6 weeks for tumor assessments + 2 x 2 weeks for permitted visit window was defined for this case of censoring.
2 Apr 2022	Derivation of primary or secondary endpoints Section 3.2.4, page 19 Section 3.2.8, page 20	The sentence 'which is the point estimate of PFS/ OS at the latest event $\leqslant$ 365 day from first dose of study treatment' were removed.	Yes	These sentences were used to specify the rules for programming. They could be written in ADaM specification instead of in SAP.
2 Apr 2022	Derivation of primary or secondary endpoints Section 3.2.5, page 19	It is emphasized that the denominator of ORR should be patients with measurable disease.	Yes	In CSP 2.0, inclusion criteria 8 was added to require that only patients with measurable disease at screening could be enrolled. And

				the definition of ORR was modified accordingly.
2 Apr 2022	Derivation of primary or secondary endpoints Section 3.2.7, page 20	The domain of possible last recorded date that an individual patient was known to be alive was clearly stated.	Yes	This clarification was to avoid ambiguous code in programming.
2 Apr 2022	Other Section 3.3.1, page 21		Yes	The derivation rules were modified according to the data actually collected in EDC.
2 Apr 2022	Data presentations Section 3.3.2, page 22	The sentence 'Laboratory data will be from local laboratories and will be converted to AZ preferred units, and AZ project reference ranges will be used for the primary interpretation of laboratory data' was deleted.	Yes	AZ will not provide preferred units and reference ranges.
2 Apr 2022	Data presentations Section 3.3.8, page 23 and page 24	ALT and AST category added >8x - ≤10x, >10x - ≤20x. Sentence 'Plots of post-baseline ALT and AST vs. post-baseline total bilirubin will also be produced with reference lines at 3×ULN for ALT, AST, and	Yes	These categories were added to show more information. Plots of potential Hy's law case were not needed.

		2×ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis' was deleted.		
2 Apr 2022	Other Section 3.3.9, page 24 Section 4.2.3, page 28	Prior medication was defined as any medication that ended prior to the first dose of the study treatment	Yes	The definition of both prior and concomitant medication was deleted.
2 Apr 2022	Other Section 3.3.10, page 24	A new section about the definition of class of anti-cancer therapy was added.	Yes	To clearly distinguish previous, concurrent and subsequent anti-cancer therapy.
2 Apr 2022	Other Section 4.1.2, page 24	The sentence 'In addition, all efficacy and safety data and some selected relevant data (eg, patient disposition, demography and baseline characteristics) will be summarised separately for the WHO/ECOG PS 0 to 1 and 2 subgroups' was modified to 'In addition, some efficacy and safety data will be summarised separately for the WHO/ECOG PS 0 to 1 and 2 subgroups'.	Yes	Not all efficacy and safety data were needed to be analyzed for PS subgroup.
2 Apr 2022	Derivation of primary or secondary endpoints Section 4.1.6, page 26	In table 5 some derivation rules were added, including: time from original diagnosis to the first dose of study treatment, time from the latest assessment to the first dose of study treatment, time to first AE, and duration of AE.	Yes	These rules were added as needed.
2 Apr 2022	Derivation of primary or secondary endpoints Section 4.1.7, page 26	The sentence 'Imputation will be done only in the context of identifying treatment emergent adverse event (TEAE)' was deleted.	Yes	The imputation of date of AE will not only be used to identify TEAE, but also for other calculations, such as time to first AE.
2 Apr 2022	Data presentations Section 4.2.2.2, page 28	Variables of pathology of SCLC at screening include time from original diagnosis to the first dose of study treatment, time from the latest assessment date to the first dose of study treatment, pathology at diagnosis with primary tumor, regional lymph nodes and	Yes	This section was modified according to actual data collected.

		distant metastases TNM classification, and stage/AJCC stage.		
2 Apr 2022	Data presentations Section 4.2.2.4, page 28	It was added that 'The event recorded in medical history page will be classified as medical history and current disease for summary. Any event that ended prior to the first dose of the study treatment will be considered as medical history. While those which ended after the first dose or are still ongoing will be considered as current disease'.	Yes	This sentence was added as demanded.
2 Apr 2022	Data presentations Section 4.2.2.5, page 28	The methods, how concurrent anti-cancer therapy and subsequent anti-cancer therapy would be analyzed, were added.	Yes	This sentence was added as demanded.
2 Apr 2022	Data presentations Section 4.2.2.6, page 28	The definition of concurrent and subsequent PCI was added.	Yes	This sentence was added as demanded.
2 Apr 2022	Derivation of primary or secondary endpoints Section 4.2.4, page 29	Time to event will be censored at the date of DCO, death, 90 days after the last dose of durvalumab treatment or the date of initiation of the first subsequent therapy, whichever occurs first. K-M curve will be presented.	Yes	The rules of censoring was more clear and involve date of DCO into consideration. K-M curve was required.
2 Apr 2022	Data presentations Section 4.2.5.4, page 30	DoR will be analysed in the same methods as PFS.	Yes	This sentence was modified to avoid unnecessary repeat.
2 Apr 2022	Data presentations Section 4.2.6.1, page 30 and page 31	The information of summary of AE and death was modified.	Yes	The section was modified as demanded.
2 Apr 2022	Data presentations Section 4.2.6.3, page 32	Shift tables for lab tests were added.	Yes	The section was modified as demanded.

2 Apr 2022	Other Section 4.2.8, page 33	Definition of subgroups were modified.	Yes	The section was modified as demanded.

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other
All the section and page no. in the second column corresponded to the location in SAP v1.0 which was finalized on 30 Oct 2020.

1 STUDY DETAILS

1.1 Study objectives

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

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

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

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

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

1.2 Study design

This will be an open-label, single-arm, multicenter, Phase IIIb study to determine the safety of durvalumab + etoposide and cisplatin or carboplatin as first-line treatment in patients with extensive stage small-cell lung cancer. Patients who fulfil all the inclusion criteria and none of the exclusion criteria will be enrolled and receive treatment with durvalumab + etoposide and either cisplatin or carboplatin (EP) for 4 to 6 cycles. Durvalumab will be administered at a dose of [redacted] every 3 weeks (Q3W) with first-line chemotherapy (EP) and will continue to be administered as monotherapy every 4 weeks (Q4W) post-chemotherapy until progressive disease (PD). Prophylactic cranial irradiation (PCI) is allowed at the investigators' discretion as per standard of care (SoC) guidance for extensive stage small-cell lung cancer (ES-SCLC). Patients will attend a safety follow up visit 90 days after last dose of durvalumab. The study flowchart is shown below in Figure 1 Overall study design.

Figure 1 Overall study design

ES-SCLC Extensive-stage small-cell lung cancer; EP etoposide + cisplatin or carboplatin; PD Progressive disease

The schedule of assessments including safety, tolerability, and efficacy using RECIST version 1.1 are detailed in the study assessment schedule in Appendix A.

Tumour assessments using computed tomography (CT)/magnetic resonance imaging (MRI) will be performed at the times specified in the schedule of assessment (Appendix A). RECIST 1.1 measurements as assessed by the Investigator will be used to derive the secondary variables of PFS, APF12, ORR, and DoR. The categorisation of objective tumour response assessment into complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or not evaluable (NE) will be based on RECIST 1.1.

Patients will be followed for survival status every 3 months (q3m) following treatment discontinuation, until death, withdrawal of consent or the end of the study. These contacts may be conducted by phone and the survival data collected will be reported in the clinical database.

1.3 Number of patients

This is a safety study and no formal sample size calculation will be done. However, assuming AE of CTCAE grade ≥3 with an incidence of 60%, approximately 300 patients are needed to achieve the estimation precision no wider than 5.7% based on exact method (Clopper-Pearson). In addition, assuming the imAE with an incidence of 20%, the estimation precision will be no wider than 4.7% using the same method. An illustration of the precision around the varying incidences of AE for the patients enrolled is provided in Table 1 Precision around varying incidence of AE.

Table 1 Precision around varying incidence of AE

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

2 ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Safety set (SS)

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

2.1.2 Efficacy analysis set

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

2.2 Violations and deviations

Protocol deviations are defined as any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are defined as a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Categories of protocol deviations and IPDs will be documented by clinical operation team. Protocol deviations and IPDs will be recorded accordingly throughout the study by clinical investigators. Several IPDs could be identified with programming to assist locating potential IPDs.

These IPDs identified by programming will be reported to clinical operation team and be combined with clinical PD findings. The final combined PDs from clinical operation team will be used for statistical analyses.

A complete list of anticipated protocol deviations (including important protocol deviations) will be compiled separately and finalised prior to database lock.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Primary endpoints

Primary endpoints include incidence of grade ≥3 AEs and incidence of imAEs.

Incidence of grade ≥3 AEs: Number and proportion of patients in SS with CTCAE (version 5.0) grade ≥3 AEs.

Incidence of imAEs: Number and proportion of patients in SS with imAEs.

imAEs: ImAEs will be identified from AEs of special interest (AESIs) based on programmatic rules that consider interventions involving systemic steroid therapy, immunosuppressant use, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as

well as treatment of symptoms resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [e.g., verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate).

3.2 Secondary endpoints

Secondary endpoints include some variables regarding the efficacy of durvalumab + EP, such as PFS, APF12, ORR, DoR using site investigator assessment and OS, OS12 and some variables regarding the safety and tolerability of durvalumab + EP, such as incidence of AEs, SAEs, AESIs and AEs resulting in treatment discontinuation.

3.2.1 Derivation of RECIST visit responses

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. It will also be used to determine, if and when a patient's disease has progressed in accordance with RECIST and their best objective response to study treatment.

The baseline radiological tumour assessment is part of the screening procedure and should be performed no more than 28 days before the start of treatment, and ideally as close as possible to the start of study treatment. Tumour assessments will be at 6 weeks ± 2 weeks after study treatment initiation, at 12 weeks ± 2 weeks after study treatment initiation and then continue every 8 weeks ± 2 weeks thereafter until disease progression. An additional follow-up scan will be performed if clinically feasible.

If an unscheduled assessment is performed, and the patient's disease has not progressed, every attempt should be made to perform the subsequent assessments at patients' scheduled visits. This schedule is to be followed to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Additional scans can be completed per standard practice post-disease progression.

From the investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD, using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

RECIST outcomes (ie, PFS and ORR etc.) will be calculated programmatically from site investigator data from overall visit responses.

3.2.2 Site Investigator Assessments Using RECIST 1.1

Site investigator will record their assessment of overall response, and response in target lesions, non-target lesions, new lesions on the CRF form. Instructions to the investigator regarding selection of target and non-target lesions are included in Appendix C of the Clinical Study Protocol.

3.2.2.1 Target Lesions

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

All other measurable lesions not recorded as TL, and all non-measurable lesions (or sites of disease) should be identified as non-target lesions (NTLs) at baseline and their response should be followed at subsequent visits.
For patients who do not have measurable disease at entry (ie, no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions. If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Missing TL Data

If all TL measurements are missing, then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

3.2.2.2 Non-Target Lesions and New Lesions.

At each visit an overall assessment of the NTL response should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

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

3.2.2.3 New Lesions

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

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

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

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response will be PD irrespective of the TL and NTL response.

Symptomatic deterioration is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

3.2.2.4 Overall Visit Response

Table 2 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 2 Overall Visit Responses

Target	Non-target	New Lesions	Overall Visit Response
CR	CR (or NA)	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**
NA	NA	No (or NE)	**NED**

CR complete response; PR partial response; SD stable disease; PD progression of disease; NE not evaluable; NA not applicable (only relevant if there were neither target nor non-target lesions at baseline); NED no evidence of disease.

3.2.3 PFS

PFS is defined as the time from first dose of study treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of tumor assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at the day of first dose unless they die within 2 visits of baseline (2 x 6 weeks for tumor assessments + 2 x 2 weeks for permitted visit window).

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

PFS (months) = (Date of event or censoring – Date of first dose + 1) /30.4375, results round to 1 decimal place. The cases of event and censoring are listed in Table 4 PFS calculation under various cases.

Given the scheduled visit assessment scheme (ie, q6w ± 2w for the first 12 weeks then q8w ± 2w thereafter) the definition of 2 missed visits will change. To evaluate the no. of missing tumor assessments between the first PD/death and the last non-missing tumor assessment before, following rules will be used.

Table 3 Criteria of at least 2 missing tumor assessments

Cases	Conditions when considered as at least 2 missing tumor assessments
There is 2 consecutive missed tumor assessments before first PD/death since first dose.	Time interval between first dose and first PD/death is >16 weeks (ie. 2 * 6 + 4 weeks, 112 days)
If the 2 consecutive missed tumor assessments occur over the period(Week 12) when the scheduled assessments changes from q6w to q8w	Time interval between the last tumor assessment and first PD/death is >18 weeks (ie. 6 + 8 + 4 weeks, 126 days)
If the 2 consecutive missed tumor assessments occur after Week 12 onwards	Time interval between the last tumor assessment and first PD/death is >20 weeks (ie. 2 * 8 + 4 weeks, 140 days)

Table 4 PFS calculation under various cases

Cases	Date used as the end of PFS	Event or Censoring
Patients with PD or death, and first PD or death are within 2 assessments after last tumor assessment before PD/death	Date of first PD or death	Event
Patients with PD or death, and first PD or death are after 2 or more missing assessments from last tumor assessment before PD/death	Date of the last non-PD tumor assessment after first dose	Censoring

Patients without PD and death but had post-treatment tumor assessment	Latest date of tumor assessment after first dose	Censoring
Patient is alive and has no tumor assessments after first dose or does not have baseline tumor data	Date of first dose	Censoring
Patient has died >16 weeks after start of treatment and has no tumor assessments after first dose or does not have baseline tumor data	Date of first dose	Censoring

3.2.4 APF12

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

3.2.5 ORR

ORR is defined as the proportion of patients with measurable disease at baseline who have at least 1 visit response of CR or PR. If any patients do not have measurable disease at baseline then the analysis of ORR will exclude these patients, so that the denominator is a subset of the SS who have measurable disease at baseline. Data obtained up to progression or last evaluable assessment in the absence of progression will be included in the assessment of ORR.

However, any CR or PR which occurred after a further anti-cancer therapy was received will not be included in the numerator for the ORR calculation (where the SS with measurable disease will be the denominator).

ORR (%) = No. of patients with CR or PR before further anti-cancer therapy after first dose /No. of a subset of SS patients with measurable disease *100, results round to 1 decimal place.

3.2.6 DoR

Duration of response is only calculated for patients who have a best overall tumor response of CR or PR before further anti-cancer therapy after first dose.

Duration of response will be defined as the time from the date of first documented response until the date of PD or death in the absence of disease progression. The end of response should coincide with the date of PD or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the date of tumor assessment for the first response of PR or CR.

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

DoR (months) = (Date of event or censoring – Date of first documented CR or PR before further anti-cancer therapy after first dose + 1) /30.4375, results round to 1 decimal place.

3.2.7 OS

Overall survival is defined as the time from the date of first dose of study treatment until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. The possible last recorded date could be found from visits, AEs, concomitant medication, cancer therapy, vital signs, physical examination, lab test, study drug exposure, survival status survey and disposition of patient.

OS (months) = (Date of death or last recorded date on which the patient was known to be alive - date of first dose of study treatment + 1) /30.4375, results round to 1 decimal place.

3.2.8 OS12

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

3.2.9 Incidence of AEs, SAEs, AESIs and AEs leading to treatment discontinuation

An AE is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

AEs will be collected from time of signing of informed consent throughout the treatment period and including the follow-up period up to 90 days after the last dose of durvalumab treatment.

An SAE is an AE occurring during any study phase (i.e. treatment, follow-up), that fulfils one or more of the following criteria:

- results in death

- is immediately life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardize the patient or may require medical
- intervention to prevent one of the outcomes listed above

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor.

The AESIs reported in the AstraZeneca-sponsored durvalumab studies are defined as AEs that have a likely inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab and requiring more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [e.g., verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate, infusion-related reactions and hypersensitivity/anaphylactic reactions).

An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which MedDRA preferred terms contribute to each AESI. A further review will take place prior to Database lock (DBL) to ensure any further terms not already included are captured within the categories. Specific terms(PT and SOC) will be defined in an external file.

AEs leading to treatment discontinuation including AEs leading to durvalumab permanently discontinuation and AEs leading to EP permanently discontinuation.

The incidence rate of AEs/SAEs/AESIs/AEs leading to treatment discontinuation (%) = No. of patients with at least one AEs/SAEs/AESIs/AEs leading to treatment discontinuation / No. of patients in SS *100, results round to 1 decimal place.

3.3 Other safety variables

[redacted]

3.3.2 Lab test

Lab test will be measured at screening and every visit during the study. The parameters to be measured are variables in hematology, clinical chemistry and urinalysis.

Hematology parameters include absolute neutrophil count (ANC), absolute lymphocyte count (ALC), haemoglobin, platelet count (PLT) and total white cell count (WBC).

Clinical chemistry parameters include albumin, lipase, alkaline phosphatase (ALP), magnesium, alanine transaminase (ALT), potassium, amylase, sodium, aspartate transaminase (AST), total bilirubin (TBil), bicarbonate, total protein, calcium, TSH, free T3 and free T4 (reflex testing only if TSH is abnormal), chloride, creatinine, gamma glutamyl transferase (GGT), urea or blood urea nitrogen (depending on local practice), glucose and lactate dehydrogenase.

Corrected calcium product will be derived during creation of the reporting database using the following formula:
Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – Albumin (g/L)] × 0.02)

Urinalysis parameters include bilirubin, ketones, blood, pH, colour and appearance, protein, glucose and specific gravity.

3.3.3 Vital signs, weight and BMI

Vital signs will be monitored at screening and at every visit during the study. Parameters include pulse rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), height, weight, BMI and body temperature.

3.3.4 Physical examinations

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

3.3.5 ECGs

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. The results include overall evaluation and its clinical significance.

3.3.6 ECOG PS

ECOG PS will be assessed at screening and at every visit during the study. The result will range from 0 to 5, while higher score represents a severer case / worse performance status.

3.3.7 Pregnancy test

Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. The result will be negative or positive.

3.3.8 Potential Hy's law case

Patients experiencing a Hy's Law incident will be tabulated and details will be included in by-patient listings. Hy's Law incidents are those cases where a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN. Please refer to Appendix B of the CSP for further instructions.

The following summaries (n, %) of the laboratory data will be used to identify cases of Hy's law: Elevated ALT, AST, and total bilirubin during the study

- ALT ≥ 3x – ≤ 5x, > 5x – ≤8x, > 8x - ≤10x, >10x - ≤20x, and >20x upper limit of normal (ULN) during the study
- AST ≥ 3x – ≤ 5x, > 5x – ≤8x, > 8x - ≤10x, >10x - ≤20x, and >20x ULN during the study
- Total bilirubin ≥2x – ≤3x, >3x – ≤5x, >5x ULN during the study
- ALT or AST ≥3x – ≤5x, >5x – ≤8x, >8x - ≤10x, >10x - ≤20x, and >20x ULN during the study
- ALT or AST ≥3x ULN and total bilirubin ≥2x ULN during the study (Potential Hy's law): The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation

Narratives will be provided in the CSR for patients who have ALT ≥ 3x ULN plus Total bilirubin ≥ 2x ULN or AST ≥ 3x ULN plus Total bilirubin ≥ 2x ULN at any visit.

Liver biochemistry test results over time for patients with elevated ALT or AST (ie, ≥ 3x ULN), and elevated Total bilirubin (ie, ≥ 2x ULN) (at any time) will be summarized. Individual patient data where ALT or AST (ie, ≥ 3x ULN) plus Total bilirubin (ie, ≥ 2x ULN) are elevated at any time will also be listed.

3.3.9 Concomitant medication

Any medications taken by the patient at any time between the date of the first dose (including the date of the first dose) of study treatment up to the date of last dose of study treatment + 90 days in the study will be considered as concomitant medication. Any medication that ended prior to the first dose of the study treatment will be considered as prior medication.

3.3.10 Anti-cancer therapy

Anti-cancer therapy in the study will be classified as previous, concurrent and subsequent anti-cancer therapy. Previous anti-cancer therapy is the anti-cancer therapy which start before the first dose of study drug. Concurrent anti-cancer therapy is the anti-cancer therapy which start after the first dose of study drug and before the last dose of study drug. Subsequent anti-cancer therapy is the anti-cancer therapy which start after the last dose of study drug.

4 ANALYSIS METHODS

4.1 General principles

4.1.1 Analysis software

SAS® v9.4 or above version will be used for statistical analysis.

4.1.2 General analysis methods

All data, demography, baseline characteristics, safety, and efficacy, will be summarized using descriptive statistics, as appropriate for the type of data, for the SS. In addition, some efficacy and safety data will be summarised separately for the WHO/ECOG PS 0, 1 and 2 subgroups.

For continuous variable, no. of non-missing patients, no. of missing patients (nmiss), mean, standard deviation (Std), median, interquartile range (Q1 and Q3), maximum and minimum values will be used to descriptive the variable. The minimum and maximum will keep the same decimal place with the raw data, while mean, median, Q1 and Q3 will keep one more decimal place, and Std will keep two more decimal places. The decimal place of above statistics will not exceed four regardless of the decimal place of raw data.

For category variable, no. of patients and proportions will be adopted. “0” will be displayed when the count was zero. The proportions are all based on the non-missing data and will keep one decimal place unless otherwise specified. Two-sided 95% confidence intervals (CIs) will be provided as appropriate.

All patients who received at least one dose of study treatment will be included in SS, which will be the primary analysis set for all analyses unless otherwise specified.

4.1.3 Hypothesis test

No hypothesis test is required for the primary endpoints, which are descriptive.

4.1.4 Baseline

The baseline of all measurements and tests will use the latest valid records before first dose of study treatment.

4.1.5 Unscheduled visits

The records in unscheduled visits will be aligned with predefined terms of measurements and tests in the study. The results will be included in the shift table of these laboratory tests and measurements. The records in unscheduled visits will also be presented in listings but not summarized by visit.

4.1.6 Data derivation rules

The data derivation rules are describe as follows:

Table 5 Variable derivation rules

Variable (unit)	Definition	Derivation rules
Age (years)	Years from birth date to informed consent	Integer part of ((date of informed consent – date of birth) / 365.25)
Time from first dose of study treatment to the date of disposition event (months)	Months from the date of first dose of study treatment to the start date of disposition event	(Start date of disposition event – date of first dose of study treatment + 1) / 30.4375, round to 2 decimal place
Time from original diagnosis to informed consent	Months from the date of original diagnosis to the date of informed consent	(Date of informed consent – date of original diagnosis) / 30.4375, round to 2 decimal place
BMI at each visit (kg/m^2)	Weight over squared height	Weight at each visit (kg) / height at screening (m)^2, round to 2 decimal place
Time from original diagnosis to the first	Months from the date of original diagnosis of SCLC	(Date of first dose of study treatment – date of original

dose of study treatment (months)	to the date of first dose of study treatment	diagnosis of SCLC + 1) / 30.4375, round to 2 decimal place
Time from the latest assessment to the first dose of study treatment (months)	Months from the date of latest assessment of SCLC to the date of first dose of study treatment	(Date of first dose of study treatment – date of latest assessment of SCLC + 1) / 30.4375, round to 2 decimal place
Time to first AE (days)	Days from the date of first dose of study treatment to the date of first AE occurrence or censoring	Date of first AE or censoring – date of first dose of study treatment +1
Duration of AE (days)	Days from the AE start date to the AE stop date or date of DCO. The date used should not be imputed.	AE stop date or date of DCO – AE start date +1

4.1.7 Handling of missing data and incomplete date

Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (i.e. below the lower limit of quantification) or >x (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug, with the exception of causality assessments that are not applicable for the patient. The original incomplete or missing dates will be presented in the listings.

- Adverse events: all AEs will be considered as treatment-emergent unless the opposite can be clearly stated.
- Concomitant medications: all medications will be considered as concomitant unless the opposite can be clearly stated.

The original incomplete or missing start dates will be imputed as below:

- Missing day: impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date
- Missing day and month: impute 1st January unless year is the same as first dose date then impute first dose date

- Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date, ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or study.

Partial AE or medication end dates will be imputed as follows:

- If only day is missing: impute day as the earlier of either the date of DCO or the last day of the month;
- If day and month are missing: impute day and month as the earlier of either the date of DCO or the last day of the year;
- If the end date is missing, then the analysis end date will not be imputed.

Imputed dates will not be used for deriving duration of events or treatment.

If a patient is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- For missing day only – using the 1st of the month
- For missing day and month – using the 1st of January

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e.

censored at the last known alive date.

4.2 Analysis methods

4.2.1 Disposition of patients

The summary table of disposition will include no. of patients screened and enrolled, and the distribution of disposition events. Reason for screening failure will also be presented.

Important protocol deviations recorded by clinical operation team will be summarized according to predefined categories. All protocol deviations will also be listed.

The number and proportion of patients included and excluded from SS will be summarized. For those excluded from SS, reasons for exclusion will be summarized.

The excluded patients will be identified on data review meeting. The reasons will be imported to analysis dataset from an external document.

4.2.2 Demographics and baseline characteristics

All the variables below will be summarized using descriptive statistics for continuous and categorical variable accordingly. Specific of other category in each variable will not be presented in summary tables but listed. Variables which are not presented in the following statements but collected in EDC will not be summarized but listed.

4.2.2.1 Demographics

Demographics includes age, age group (<65 years, ≥65 years), sex, race, ethnicity, height, weight and body mass index (BMI) at screening.

4.2.2.2 Pathology at screening

Variables of pathology of SCLC at screening include time from original diagnosis to the first dose of study treatment, time from the latest assessment date to the first dose of study treatment, pathology at diagnosis with primary tumor, regional lymph nodes and distant metastases TNM classification, and stage/AJCC stage.

4.2.2.3 Extent of SCLC upon entry to study

Variables of extension of disease upon entry to study include whether the patient had recurrence of earlier cancer and sites of local/metastatic disease.

4.2.2.4 Medical and surgical history

Variables to describe medical history include no. of patients with any medical history and coded terms of medical history. The terms of medical history will be coded using the latest version of MedDRA before database lock. The coded terms will be sorted according to the descending order of occurrence rate of system organ class (SOC) and preferred term (PT) within each SOC.

The event recorded in medical history page will be classified as medical history and current disease for summary. Any event that ended prior to the first dose of the study treatment will be considered as medical history. While those which ended after the first dose or are still ongoing will be considered as current disease.

Surgical history will be summarized in the same way as medical history.

4.2.2.5 Anti-cancer therapy

Number and percentage of patients had previous cancer therapy will be summarized. The therapy class, therapy agent and with or without concomitant chemoradiotherapy will be listed.

Concurrent and subsequent anti-cancer therapy will be summarized separately in the same way as previous anti-cancer therapy.

4.2.2.6 Radiotherapy

Number and percentage of patients had previous radiotherapy will be summarized. Other variables including site, start date, end date, etc. will be listed.

Concurrent and subsequent radiotherapy will be summarized separately in the same way as previous radiotherapy.

Number and percentage of patients receiving concurrent/ subsequent PCI will be summarized and listed. Other concurrent/ subsequent radiotherapy will be summarized in the same way as PCI. Concurrent/ subsequent PCI is the concurrent/ subsequent radiotherapy whose site or region is brain and treatment status is prophylaxis.

4.2.2.7 Use of nicotine

Nicotine use, category (never, former, current) and number of pack years used will be summarized.

4.2.3 Prior and concomitant medications

Any medications taken by the patient at any time between the date of the first dose (including the date of the first dose) of study treatment up to the date of last dose of study treatment + 90 days in the study will be considered as concomitant medication. Any medication that ended prior to the first dose of the study treatment will be considered as prior medication.
No. of patients with any prior or concomitant medications will be presented. Medications will be presented and coded using WHO Drug dictionary (WHO DD) and sorted by descending order of occurrence rate.

4.2.4 Primary endpoints

Adverse events, which start after first dose of study drug up to 90 days after the last dose of durvalumab treatment or the date of initiation of the first subsequent therapy, whichever occurs first, will be analysed in summary table. Other AEs recorded in the study will only be listed. This rule applies to all analysis of AE.

Frequency of AEs of CTCAE grade ≥3, no. and percentage of patients with AEs of CTCAE grade ≥3 will be presented. These AEs will also be summarized by System Organ Class (SOC) and preferred term (PT). The exact 95% CIs around the incidence estimates will also be reported.

Time to event endpoints will be analysed using Kaplan-Meier method to estimate the median event time to the first AE of CTCAE grade 3 or higher. If a patient has no AE of CTCAE grade 3 or higher, the time to event will be censored at the date of DCO, death, 90 days after

the last dose of durvalumab treatment or the date of initiation of the first subsequent therapy, whichever occurs first. K-M curve will be presented.

Similar analyses will be conducted for imAEs.

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. In general, imAEs will include AESIs that are managed using steroids, immunosuppressants and/or hormone replacement therapy.

The identification of imAEs will be made following the AstraZeneca imAE characterization charter.

1. The selection of preferred term,
2. Programmatic identification of those potential imAEs requiring medication such as steroids, immunosuppressants and/or hormone replacement therapy

All imAEs which are identified by the investigator (as recorded in CRF Adverse Events (AE)) will undergo a review by medical monitor. In addition, imAEs will be checked programmatically as described in the imAE charter on the clinical database to ensure the recording of imAEs are complete and unambiguous. If any discrepancies found, those will be resolved as an on-going basis and before DBL.

All above AEs will be listed.

4.2.5 Secondary endpoints

4.2.5.1 PFS

PFS will be summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% CIs, given the anticipated maturity of 60%. The Kaplan-Meier curves will be provided. The no. and proportion of cases of events (e.g. PD, death) and censorings will be summarized.

4.2.5.2 APF12

APF12 will be estimated using the Kaplan-Meier curve. The estimate along with confidence intervals using Greenwood's estimate of standard error and a log-log transformation will be presented.

4.2.5.3 ORR

ORR will be summarized descriptively, and the exact 95% CIs will be provided. Best overall response before a further anti-cancer therapy in the study will be summarized. No. and proportion of patients with each kind of best overall response will be presented.

4.2.5.4 DoR

Kaplan-Meier plot will be produced using the same methods as PFS whenever appropriate. Otherwise, descriptive statistics will be presented.

4.2.5.5 OS

OS will be analysed in the same methods as PFS.

4.2.5.6 OS12

OS12 will be analysed in the same methods as APF12.

4.2.5.7 Incidence of AEs, SAEs, AESIs and AEs leading to treatment discontinuation

Analyses similar to the primary endpoints will be conducted for overall AEs, SAEs, AESIs and AEs leading to discontinuation of study treatment. In addition, the no. and percentage of patients with AEs will be presented by PT.

All above AEs will be listed. Detailed statement of death will be listed.

4.2.6 Other safety variables

4.2.6.1 Adverse Events

The following AE summaries will be summarized similar to the primary endpoints:

- All AEs causally related to any study treatment
- All AEs by CTCAE grade
- Any CTCAE grade ⩾3 causally related to any study treatment
- All SAEs causally related to any study treatment
- All AESIs causally related to any study treatment
- AEs leading to discontinuation of any study treatment, causally related to any study treatment
- AEs that resulted in death
- AEs that resulted in death causally related to any study treatment
- Other significant AEs

AE, AE with CTCAE grade ≥3, AESI and imAE will be summarized by SOC, PT and most severe outcome. The severity of outcome is Fatal> Not Recovered/Not Resolved> Recovered/Resolved with Sequelae> Recovering/Resolving> Recovered/Resolved.

Most common AEs (≥2%), most common AEs of CTCAE grade 3 or 4, causally related AEs, causally related AEs of CTCAE grade 3 or 4, AEs leading to interruption of durvalumab/EP/study treatment, SAEs, SAEs causally related to study treatment will also be summarized for PT and maximum CTCAE grade.

A summary of deaths will be provided with the following information:

- Total number of deaths (regardless of date and reason of deaths)
- Death related to disease under investigation only, as determined by the investigator
- Deaths related to disease under investigation, as determined by the investigator, and with an AE with outcome of death (with further subcategories for AEs with onset/worsening date prior to 90 days after the last dose of study treatment and initiation of subsequent anticancer therapy)
- AEs with outcome of death only (with further subcategories for AEs with onset/worsening date prior to 90 days after the last dose of study treatment and initiation of subsequent anticancer therapy)
- Other deaths

A list of all deaths will also be produced.

Any AE with a relatedness to study treatment of possible or probable will be considered to be causally related to study treatment for purposes of the data summaries. Relatedness should be assigned by the investigator to each study treatment individually on the eCRF. When the relatedness of an AE is missing on the eCRF, all efforts will be taken to ensure that the Investigator assigns his/her assessment of relatedness prior to database lock.

If relatedness of an AE is missing at the DBL, the AE will be considered as related to study treatment and related to durvalumab.

4.2.6.2 Exposure

The exposure for durvalumab and each kind of drug of EP will be summarized respectively.

- intended exposure for durvalumab
- actual exposure for durvalumab
- total number of cycles of each molecule received
- number of patients receiving 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, >12 cycles of durvalumab
- number of patients receiving 1, 2, 3, 4, 5, 6, >6 cycles of each drug of EP
- number of, and reasons for, dose delays and interruptions

Additionally, for durvalumab, relative dose intensity will also be summarized.

Dose reductions are not permitted per the CSP for durvalumab and the actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

All these variables will be listed. Overdose report will also be listed.

4.2.6.3 Lab tests

Baseline and post-baseline hematology, clinical chemistry and urinalysis results will be summarized descriptively by visit according to the general principles. For continuous laboratory assessments, absolute value and change from baseline will be summarized using descriptive statistics at each scheduled assessment time. These data summaries will be

provided in international system (SI) of units whenever applicable. The frequency and percentage for each clinical evaluation category (e.g., 'normal' and 'abnormal with/without clinical significance', 'Unchecked') will be summarized by visit. Shift table will be provided to show the change in CTC (V 5.0) grades between baseline and the worst post-baseline case if applicable. For the tests in clinical chemistry without CTC grade, shift table will be provided to show the change from baseline to maximum and minimum value during treatment respectively. For the tests in urinalysis, shift table will be provided to show the change from baseline to the worst value on treatment. Only when there is no post-baseline CTC grades or values, the worst post-baseline/ maximum value/ minimum value of lab test will be considered as unchecked in shift table. For the lab tests in clinical chemistry which have no CTC grades, normal range (low, normal, and high) will be used to evaluate the maximum or minimum value.

Listings will be provided for those whose results are normal at baseline and abnormal in post-baseline evaluations, or abnormal both at baseline and in post-baseline evaluations.

4.2.6.4 Vital signs, weight and BMI

Baseline and post-baseline vital signs, weight and BMI will be summarized descriptively by visit. Change from baseline at each visit will also be summarized. Box plots of the vital signs results by visit will be presented.

All baseline and post-baseline vital signs, weight and BMI will be listed.

4.2.6.5 Physical examinations

Patient with PE in the study will be listed.

4.2.6.6 ECGs

The change from baseline ECG evaluation to post-baseline ECG evaluation will be summarized using shift table. The worst case will be used as post-baseline result for analysis. Only when there is no post-baseline clinical evaluation, the worst post-baseline of ECG evaluation will be considered as unchecked in shift table.

Patient with abnormal ECG results in the study will be listed.

4.2.6.7 ECOG PS

A summary of ECOG performance status at each scheduled time point will be provided.

ECOG PS in the study will be listed.

4.2.6.8 Pregnancy test

Patients with positive baseline or post-baseline pregnancy test results will be listed.

4.2.6.9 Potential Hy's Law case

Liver diagnosis, liver risk factors and liver signs and symptoms regarding PHL case will be listed by patient and PHL case.

4.2.7 Subsequent anti-cancer therapy

Subsequent anti-cancer therapy is the anti-cancer therapy which start after the last dose of study drug. Variables of subsequent anti-cancer therapy will include no. of patients with anticancer therapy post IP, therapy class, therapy agent and no. of cycles. These variables will be summarized using descriptive statistics for continuous and categorical variable accordingly.

4.2.8 Subgroup analysis

Subgroup analysis of safety and efficacy (i.e. primary and secondary endpoints) will be conducted for the cohorts of patients with PS 0, 1, and 2 at baseline. For time to event analysis, each subgroup must have at least 20 events per subgroup level in order for that subgroup level to be included in the subgroup analysis.

Additional subgroup analyses may be conducted for primary and/or secondary endpoints based on the following:

- Platinum therapy administered in cycle 1 (cisplatin vs carboplatin)
- Sex (male versus female)
- Age (<65 versus ≥65 years of age)
- Smoking status (current and former versus never smoker)
- Number of cycles of EP (≤4 versus >4, based on etoposide exposure)
- Use of PCI (yes versus no)
- Brain metastases (yes versus no)
- Liver metastases (yes versus no)
- AJCC stage (stage III versus stage IV)

Patients with missing data for a subgroup variable will be excluded from the analysis for that subgroup only.

4.2.9 Sensitivity analysis

Considering the IPDs which could significantly affect the evaluation of efficacy endpoints may occur in the study, sensitivity analysis will be performed for PFS and OS excluding the patients with such IPDs.

These IPDs will be determined in the date review meeting before database lock and clearly documented.

5 INTERIM ANALYSES

There will be no formal interim analysis in this study.

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

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

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

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

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

6 CHANGES OF ANALYSIS FROM PROTOCOL

No change of analysis from protocol is made.

7 REFERENCES

None.

8 APPENDIX

Appendix A Schedule of assessments

Visit	**Screening**	**Treatment period**			**Safety follow-up visit**	**Survival follow-up phone calls/emails**
		Baseline (Day1)	**During Chemotherapy** 1 cycle = 21 days	**Post-Chemotherapy** 1 cycle = 28 days		
Visit window	**Day-28 to Day-1**	**0**	**±3 days**	**±3 days**	**±7 days**	**±14 days**
Week	**Weeks-4 to Week-1**	**Week 0**	**Week 3, 6, 9; Weeks 12, 15 at investigator discretion**	**3 weeks after last dose of chemotherapy (either Week 12, 15 or 18), then every 4 weeks until PD**	**90 days after last dose**	**Every 3 months**
Written informed consent[a]	X					
Inclusion/exclusion criteria	X					
Demographics, including baseline characteristics	X					
Medical history, including cancer treatment history	X					

Visit	**Screening**	**Treatment period**			**Safety follow-up visit**	**Survival follow-up phone calls/emails**
		Baseline (Day1)	**During Chemotherapy** 1 cycle = 21 days	**Post-Chemotherapy** 1 cycle = 28 days		
Visit window	**Day-28 to Day-1**	**0**	**±3 days**	**±3 days**	**±7 days**	**±14 days**
Week	**Weeks-4 to Week-1**	**Week 0**	**Week 3, 6, 9; Weeks 12, 15 at investigator discretion**	**3 weeks after last dose of chemotherapy (either Week 12, 15 or 18), then every 4 weeks until PD**	**90 days after last dose**	**Every 3 months**
ECG recording[b]	X	As clinically indicated				
Physical examination, weight, and vital signs	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	
Laboratory Assessments						
Clinical chemistry[c]	X	X[d]	X	X	X	
Hematology[c]	X	X[d]	X	X	X	
TSH, (reflex free T3 or free T4[f])	X	X[e]	X	X	X	
Hepatitis B, C, HIV virology	X					
Pregnancy test[g]	X	X	X	X	X	
Urinalysis	X	As clinically indicated				
Monitoring						
AE	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	
IP Administration						
Durvalumab [h]		X	X	X		
Etoposide [i]		X	X [k]			
Carboplatin or cisplatin [i,j]		X	X [k]			

Visit	**Screening**	**Treatment period**			**Safety follow-up visit**	**Survival follow-up phone calls/emails**
		Baseline (Day1)	**During Chemotherapy** 1 cycle = 21 days	**Post-Chemotherapy** 1 cycle = 28 days		
Visit window	**Day-28 to Day-1**	**0**	**±3 days**	**±3 days**	**±7 days**	**±14 days**
Week	**Weeks-4 to Week-1**	**Week 0**	**Week 3, 6, 9; Weeks 12, 15 at investigator discretion**	**3 weeks after last dose of chemotherapy (either Week 12, 15 or 18), then every 4 weeks until PD**	**90 days after last dose**	**Every 3 months**
Tumor assessment per Investigator - report (according to RECIST1.1)[l]	X	On study tumor assessments should occur at Week 6±2 weeks, at Week 12±2 weeks then every 8±2 weeks[m] until PD				
Subsequent anticancer therapy					X	X
Survival status					X	X

a. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of first dose.
b. Any clinically significant abnormalities detected require triplicate ECG results.
c. Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.
d. If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at day 1.
e. If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
f. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
g. Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.
h. Results for liver function tests, electrolytes, full blood count, and creatininemust be available before commencing an infusion (samples taken within 3 days prior to infusion) and reviewed by the treating physician or Investigator prior to dosing.
i. Durvalumab will be administered first, followed by the etoposide + cisplatin/carboplatin regimen.
j. If cisplatin, infuse over 1 to 2 hours. If carboplatin, infuse over 0.5 to 1 hour.
k. Chemotherapy regimen (etoposide plus either cisplatin or carboplatin) to be administered Q3W for 4 to 6 cycles, per investigator clinical decision.
l. See protocol Section 6.1 and Appendix C for additional details relevant to image acquisition, RECIST 1.1 assessments, and evaluation of scans after RECIST 1.1-defined progression.
m. Patients will have scans done Q6W for the first 12 weeks, and then Q8W thereafter or per institutional standard at investigator discretion.

Appendix B TFL mock shells

Please refer to the independent appendix document containing all TFL mock shells.

Appendix C SDTM and ADaM specifications

Please refer to the independent appendix documents for the specifications.